



Otto Mauvert, N. D.



A CONCISE TREATISE ON MEDICINAL HERBS,
THEIR USEFULNESS AND CORRECT
COMBINATION IN THE TREAT-
MENT OF DISEASES.



A GUIDE TO HEALTH BY NATURAL MEANS



*With Many Black and
Colored Illustrations*



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PREFACE

 F late years there has been a growing demand from all sections of the country, by persons who are interested in Natural means of combating disease, for a book, which would give a concise, yet comprehensive treatise on Medicinal Plants, their use and their compatible combinations.

This book has been written to fill that need. It represents years of painstaking accumulations of data based upon practical experience.

I think it is, however, appropriate to explain with a few introductory words why Herbs are better suited for the treatment of diseases than chemicals and other substances foreign to the human body.

Herbs are the product of Nature, containing many substances very finely distributed, which are necessary for building up and maintaining the organs of the body, and are of the greatest help in the performance of the vital functions.

They contain these substances partly in the same condition as they are present in the human system, allowing direct assimilation, and partly so that they can be readily taken up in the circulation of the blood, after undergoing certain changes in the digestive tract.

Chemistry of today has accomplished wonderful results in many ways, but all the laboratories in the world will never be able to supplant the remarkably fine process which takes place in the living cell; they will never successfully imitate the wonderful methods that Nature uses in performing its work in the plant, as well as, in the human body. Our late American wizard, Thomas A. Edison, expressed himself on this subject as follows: "Until man duplicates a blade of grass, Nature can laugh at his so-called scientific knowledge."

Remedies made from chemicals and minerals will never stand in favorable comparison with the products of Nature—the living cell of the plant, the final result of the rays of the sun, the mother of all life.

It is true that our body contains minerals, but the minerals cannot be taken up directly by the system, they must be obtained from a living cell of either plant or animal life.

Plants have the power of taking up mineral substances through their roots from the soil and assimilate and transform them in such a way that they may be utilized by the organs of the human body, thus becoming useful as food, as well as, medicine.

The human body, on the other hand, has not the ability of directly assimilating mineral substances and therefore cannot utilize them in any way.

By making this comparison, which truth cannot be denied, we can understand why a harmless herb has often a stronger and more beneficial effect than the strongest chemical.

This has also been conclusively proven by the newest discoveries of the different Vitamins, substances which, although they are contained only in very small quantities in plant and animal life, are essential constituents in the food, performing vital function in the system. These vitamins are entirely lacking in minerals.

Animal and human bodies are composed of certain well defined elements, in certain well defined proportions. If any of these elements are present in over-abundance and others are partly or wholly lacking, an abnormal condition will be brought about, causing disease.

This lack or deficiency of these vital elements, or the over-abundance, cannot be balanced by administering mineral substances that cannot be taken up by the system. It would be as ineffective as trying to fill a sieve by pouring water through it.

Herbs contain the vital elements—Vitamins and Organic Minerals—that are deficient or lacking in the diseased body. They contain them in such finely distributed and prepared state that they may be readily assimilated by the system and conveyed to the blood.

Herbs also promote the elimination of waste matter and poisons from the system by simple, natural means.

When correctly used they support Nature in its fight against disease; while chemicals, not being assimilable, add to the accumulation of morbid matter and only simulate improvement by suppressing the symptoms.

Natural remedies are only those which Nature produces and botanical medication is the oldest branch of medicine. It undoubtedly suggested itself to man instinctively, and there is nothing mysterious about medicinal plants. They are God's gift to man—for him to use.

"And God said, Behold, I have given you every herb bearing seed, which is upon the face of the earth, and every tree, in which is the fruit of a tree yielding seed; to you it shall be meat.

"And to every beast of the earth, and to every fowl of the air, and to everything that creepeth upon the earth, wherein is life, I have given green herb for meat: and it was so." Genesis 1:29, 30.

"He caused the grass to grow for cattle, and the herb for service of man: that he may bring forth food out of the earth." Psalms 104 Verse 14.

"—And the fruit thereof shall be for meat, and the leaf thereof for medicine"—Ezekiel 47:12

Health is within your grasp—reach for it. Perhaps it will be an effort at the beginning; perhaps it will take a little longer than you would like, but in the end, your efforts will be crowned with that energy that radiates from a healthy body and which spells Success and Happiness.

A word of caution is appropriate at this time: Be sure to obtain your supply of herbs from a reliable source. To obtain the maximum good results, herbs should be fresh and true to type.

The herbs mentioned in this book should be obtainable in any first class Drug Store. If unable to procure them in your neighborhood, they may be obtained in best quality and at reasonable prices at Nature's Herb Co., 1116 Market St., San Francisco, Calif. (See ad in rear of book.)

Yours for Good Health,
THE AUTHOR.

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TABLE OF CONTENTS

	Page
Preface	1
Symptoms and What They May Mean.....	7
Diseases, Their Symptoms and Suggested Remedies	12
Formulas	52
Key to Abbreviations of Medicinal Properties	120
Materia Medica Index	122
Materia Medica	128
Index .. .	191

TABLE OF ILLUSTRATIONS

	Plate	Page
Almond		167
Aloe.....	3	62B
Arbutus Trailing.....		175
Arnica.....	3	62B
Basil, Sweet	6	30B
Birch.....		129
Blackberry.....	6	30B
Blackthorn. ..	3	62B
Bloodroot.		131
Boneset.....		131
Brier Rose	4	94A
Broom.....		132
Buckbean.....	2	94B
Buckthorn.....	5	30A
Burdock.....	1	62A
Centaury.	6	30B
Chamomile	4	94A
Chicory	1	62A
Coltsfoot	6	30B
Comfrey.....	5	30A
Cowslips.	4	94A
Cranesbill	2	94B
Dwarf Elder.....	3	62B
Dwarf Nettle.....	2	94B
Elder, European.....	2	94B
Eyebright	5	30A
Flax.....	5	30A
Gentian.. . . .	5	30A
Ginseng.....	5	30A
Golden Seal.....	4	94A
Grindelia		167
"	5	30A
"	1	62A
"	5	30A
"	4	94A

SYMPTOMS AND WHAT THEY MAY MEAN

PAIN IN THE HEAD—HEADACHES.

The underlying cause for this pain can often be found in: Disorders of the Stomach, Constipation, Anemia, Menstrual Irregularities, Overfilling of the Venous blood vessels of the head, Eye Strain, and disturbances of the functions of the Lungs and Heart.

PAIN IN THE BACK AND HIPS.

These pains are often observed in: Articular Rheumatism, Pain over the whole spinal column, In Lumbago (Pain confined to the lumbar region); In Kidney Diseases (Pain in the middle or lower part, in the right or left side from the spine), In Gallstones or Inflammation of the Gallbladder, the pain extends from the lowest rib on the right side towards the right shoulder blade; Pain in the Hips generally indicate affections of the Ovaries; Fallopian Tubes, Uterus, Rectal diseases and Hemorrhoids

PAIN IN THE CHEST.

In Pleurisy the pain is sharp and stinging, especially when taking a deep breath, with low fever generally present In Pneumonia with a dry, painful, hacking cough and high fever and chills
In Neuralgia or Rheumatism, pressure increases the pain; breathing sometimes is painful.

In Shingles: Severe neuralgic pains with a vesicular bright red eruption on the inflamed skin.

PAIN IN THE STOMACH.

In Gastritis, the pain is gnawing and burning at the pit of the Stomach after eating (so called heartburn) with gas present and a tenderness in the epigastric region. Vomiting may occur at times, but without giving relief from pain, slight fever may be noticed.

In Dyspepsia: Pain as in Gastritis but less severe, no fever, tenderness absent, vomiting occurs occasionally, which gives relief from pain.

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Rundles, Ralph W, M.D.	Durham, N C.
Samuels, Leo, Ph D	Salt Lake City, Utah
Schroeder, Henry A, M D	St Louis, Mo.
Schwartz, Steven O, M D	Chicago, Ill.
Scott, William Wallace, M.D	Baltimore, Md.
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TeLinde, Richard W, M D.	Baltimore, Md.
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Werner, Sidney C, M D	New York, N. Y.
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Wintrobe, Maxwell Myer, M D.	Salt Lake City, Utah
Witebsky, Ernest, M D	Buffalo, N. Y.
Wolman, Irving J, M D	Philadelphia, Pa.
Woolf, Ralph B, M D.	St Louis, Mo.
Woolley, George, M D	New York, N Y.
Wright, Irving S, M D.	New York, N. Y.
Zopf, Louis C, M.S.	Iowa City, Iowa

Drugs Omitted from N.N.R. 1955

The drugs listed below appeared in *N.N.R. 1954* but do not appear in the present edition because they now are considered either sufficiently well known to warrant their exclusion or because they no longer are considered useful by the Council. Well-known drugs that are considered useful are listed in the index of *N.N.R.* with a reference to the last edition in which their actions and uses appeared.

Aminophylline-U S P
 Ascorbic Acid-U S P (Cebione, Cevex)
 Carbarsone-U S P
 Carotene
 Dihydromorphinone Hydrochloride-U S P (Dilaudid Hydrochloride)
 Dipiperidon Hydrochloride (Diothane Hydrochloride)
 Dipiperidon with Hydroxyquinoline Benzoate (Diothane with Oxyquinoline Benzoate)
 Diphtheria Toxoid, Alum Precipitated-U S P.
 Iodohippurate Sodium (Hippuran)
 Iodopyracet [Iodopyracet Injection-U S P] (Diodrast)
 Phenylephrine Hydrochloride-U S P (Isophrin Hydrochloride, Neo-Synephrine Hydrochloride)
 Piperocaine Hydrochloride-U S P (Metycaine Hydrochloride)
 Sodium Iodomethamate-U S P (Neo-Iopax)
 Sodium Morrhuate [Sodium Morrhuate Injection-U S P]

The drugs listed below appeared in *N.N.R. 1954* but were omitted from the present edition because the manufacturers of the only Council-accepted dosage forms of these products discontinued their manufacture.

Fibrin Foam
 Hexethal Sodium (Ortal Sodium)
 Meralluride-U S P (Mercurhydrin)
 Mestibol (Monomestrol)
 Prophepyridamine (Trimeton)
 Sodium Ricinoleate (Soricin)
 Suramin Sodium (Naphuride Sodium)
 Urganin

Purposes and Activities of the Council on Pharmacy and Chemistry

The Council on Pharmacy and Chemistry was created in 1905 as a standing committee, appointed by the Board of Trustees of the American Medical Association to consider medicinal and allied preparations offered for prophylactic, diagnostic or therapeutic use by the physician.

The primary purpose of the Council is to encourage the practice of rational therapeutics. To achieve this objective the Council prepares special treatises, articles, status reports and books designed to give authoritative information on therapeutics to the medical profession. The Council also encourages research in therapeutics by giving grants-in-aid, by arranging therapeutic trials of promising new preparations and by stimulating basic research on fundamental problems.

It is recognized that the public has a legal right to practice self-medication, but the Council believes that only certain products may be so used with reasonable safety and intelligence. These products are defined in the rules.

In general the Council disapproves of the advertising of medicinal preparations to the public for treatment of disease conditions for the obvious reason that it promotes dangerous self-medication. Misdirected and inadequate treatment, both internal and external, failure to recognize serious disease until too late for effective treatment, the spread of infectious disease when hidden from the physician, description of symptoms in advertising leading to erroneous self-diagnosis, unconscious formation of drug habit and the possibilities of inducing allergic and other undesirable reactions of the skin and other organs are potential hazards created by inadvisable self-treatment. These dangers apply similarly to the naming of diseases and therapeutic indications on labels that may fall into the hands of the patient. However, the Council recognizes that certain label instructions are necessary for the safe and proper use of those articles defined in the rules as safe to advertise to the public.

OFFICIAL RULES GOVERNING THE ADMISSION OF ARTICLES AND EXPLANATORY COMMENTS

The principles and policies of the Council that govern the acceptance of articles for inclusion in *New and Nonofficial Remedies* are expressed in the following Official Rules and Explanatory Comments. Acceptance of an article by the Council is not to be interpreted as either an endorsement or a recommendation for its use; it means merely that the product has been found to conform to the Council's rules.

Accepted products whose promotion, usefulness or quality brings them in conflict with the rules are subject to withdrawal of acceptance and omission from *New and Nonofficial Remedies*.

Rules Governing Acceptance

RULE 1.—Scope.—Any medicinal article which, in the judgment of the Council, is considered useful in the treatment, prevention or diagnosis of human disease is eligible for consideration for inclusion in *New and Nonofficial Remedies*.

Compliance with Laws.—The responsibility for compliance with federal, state and municipal laws and regulations rests with the firm submitting an article.

Commercial Availability.—An article must be commercially available

session

Mixtures.—Mixtures of drugs are eligible for inclusion in *New and Nonofficial Remedies* providing they meet the requirements listed on page xxxvi under Criteria for the Evaluation of Certain Products

Topical Vehicles.—Vehicles, such as ointment bases, which are considered suitable for the incorporation of topical medication, are eligible for inclusion in *New and Nonofficial Remedies*, providing such vehicles are marketed separately for compounding prescriptions and/or for manufacturing use. When such products are sold for manufacturing use only, they are not eligible for inclusion or retention in *New and Nonofficial Remedies* after the formula is admitted to either the *U S Pharmacopeia* or the *National Formulary*.

Experimental and Dangerous Drugs.—Articles that have only experimental usefulness or whose use involves dangers and disadvantages outweighing their therapeutic value are considered ineligible for inclusion in *New and Nonofficial Remedies*.

Bulk Drugs.—Accepted drugs marketed in bulk for compounding prescriptions are eligible for inclusion in *New and Nonofficial Remedies*. Accepted drugs supplied in bulk form for manufacturing use only may be included in *New and Nonofficial Remedies*; but should such drugs become official, the bulk forms will be deleted from *New and Nonofficial Remedies*. Such acceptance should not be construed as extending to dosage forms of the accepted drug intended for distribution to physicians.

Rejected Drugs.—Previous noncompliance with the rules does not preclude favorable consideration of an article at a later date if adequate evidence to overcome the original objections is submitted.

Official and Nonofficial Drugs.—An official drug is described in either the *U. S. Pharmacopeia* or the *National Formulary*; a non-official drug is not so described.

Re-evaluation.—An accepted or exempted drug may be re-evaluated by the Council at any time for compliance with existing rules and usefulness in medicine.

Exemption of Well-Known Drugs.—When the actions, uses and dosage of any drug become sufficiently well known in the opinion of the Council to make a full description in *New and Nonofficial Remedies* unnecessary for the information of the medical profession, the article may be declared exempt from further description. This does not apply if new uses of the drug or special methods of administration are introduced, which in the opinion of the Council justify discussion in the current *N. N. R.* In such cases, the drug or the special dosage form may be retained or restored to *N. N. R.* for an additional period not to exceed 5 years. If the novelty applies only to the dosage form, the discussion will be restricted to this form, with reference to the last edition containing a general discussion of the drug.

Exemption of Official Drugs.—Drugs in the *U. S. Pharmacopeia* or *National Formulary* or their equivalents automatically become exempt at the expiration of 20 years' inclusion in either of the official publications or in *New and Nonofficial Remedies*. The 20-year period is computed from the year when the drug first was included in one of these three publications.

Re-evaluation of Nonofficial Drugs.—Nonofficial drugs automatically become subject to re-evaluation on the same basis as newly submitted drugs at the expiration of 20 years' inclusion in *New and Nonofficial Remedies*. Firms are required to submit evidence of continued usefulness in medicine for products of their manufacture.

Exemption of Re-evaluated Nonofficial Drugs.—Re-evaluated non-official drugs that are considered still useful in the opinion of the Council shall be exempted as sufficiently well known. When exempted, nonofficial drugs will be retained in *Tests and Standards for New and Nonofficial Remedies*, but their actions, uses and dosage monographs will be deleted. When re-evaluated drugs are considered no longer useful, all information on them is subject to omission from *New and Nonofficial Remedies*.

Brand and Generic Names of Exempt Drugs.—The brand and generic names for exempt drugs will be listed in the general index.

with a reference to the last edition of *New and Nonofficial Remedies* in which actions, uses and dosage are described

Change in Official Status.—Accepted or exempted articles containing drugs that are deleted from the *U. S. Pharmacopeia* or *National Formulary* are automatically subject to re-evaluation by the Council.

Ineligible Articles.—The Council does not consider for inclusion in *New and Nonofficial Remedies* articles that do not have direct medicinal significance, for example:

- 1 Chemical reagents and such insecticides, disinfectants and other substances as are not employed in or on the human body.
- 2 Soaps or detergents for simple cleansing purposes
- 3 Surgical and hospital supplies, instruments or mechanical devices, appliances and other nonmedicinal articles

RULE 2.—Evidence.—*Evidence of usefulness satisfactory to the Council must be presented for each new article submitted or for new or extended claims for accepted products.*

Responsibility for Evidence.—The firm that submits a new product or presents a new or extended claim for an acceptable or previously rejected product must bear the responsibility of supplying acceptable evidence to support the proposed claims.

Amount and Type of Evidence Required

New Articles.—For new articles, both animal and clinical data should be supplied. The plan of study, the number of observations, animals and patients should be such as to permit sound conclusions with respect to proposed clinical uses. The quality of evidence is quite as important as the quantity and in this respect the importance of suitable controls is emphasized. Statistical methods for designing the plan of study and for analyzing data should be employed when they are applicable. Particularly in clinical studies where interpretations are based on subjective evidence, supporting or confirming evidence from independent groups of investigators may be necessary.

Previously Accepted Articles.—Additional brands of articles included in *New and Nonofficial Remedies* or their equivalent counterparts are eligible for consideration without presentation of evidence when the claims do not exceed those recognized by the Council as published in *New and Nonofficial Remedies*. However, salts or esters of an accepted drug may be regarded in some instances as new articles.

Before new or extended claims or changes in dosage of accepted or exempt products may be made, evidence adequate to cover all proposed uses or changes should be submitted and found acceptable by the Council.

RULE 3.—Composition.—*The composition of articles submitted for inclusion in New and Nonofficial Remedies must be stated quantitatively whenever possible, with the understanding that complete formulas or their essential portions are subject to publication by the Council.*

Secrecy.—Physicians should know what they are prescribing. Unrevealed formulas or methods of treatment hamper the advance of scientific medicine and such practice cannot be defended as a means to protect a discovery. Therefore, the Council will not accept any product, the composition of which is not revealed.

Label Requirements.—Labels for submitted preparations must bear information to indicate the quantity of the active ingredients. Separately marketed topical vehicles should be labeled to indicate the quantity of each of the major components, including those that may exert any local effect upon the skin or mucous membranes or that may influence the action of any ingredient. The source of animal and vegetable proteins utilized in parenteral products must be declared on the label.

The labels or labeling also should bear such information concerning any other components that are deemed essential for the safe and intelligent use of accepted products.

Changes in Composition.—Any alterations in the composition of an accepted product and the reasons for such change must be brought promptly to the attention of the Council.

RULE 4—Tests and Standards.—*Suitable tests and standards must be submitted to establish the identity, purity, tolerances and potency of the active ingredients and of the finished product.*

Errors in Manufacture or Labeling.—A firm with an accepted product is held responsible for immediately notifying the Council of errors in compounding, sterilization or labeling which are discovered after release for distribution into commerce.

RULE 5—Nomenclature—*A trade name is acceptable for each brand of a drug, mixture of drugs or separately marketed vehicle if it is not therapeutically suggestive nor pre-empted by prior official status, and if the appropriate official or generic designation for the drug is distinctly displayed with it.*

Definitions.—For the purposes of this rule, the following definitions have been adopted.

Brand Name—A "brand name" is the trade or protected name applied to a single drug, mixture of drugs or separately marketed vehicle as supplied by one firm (For instance, in the case of a single drug, Artisal might be a brand name of a firm for its phenobarbital; in the case of a mixture, Sulozine might be a brand name for a firm's combination of sulfadiazine and sulfamerazine; in the case of a topical vehicle, Olafene might be the brand name for one firm's ointment base.) Brand names as applied to specific drugs or topical vehicles should not be confused with a general "brand mark" or trade symbol used to identify all the products of one firm nor with a "line name" used to designate a group of related drug preparations as supplied by a single firm. General brand marks or symbols, used to identify a firm rather than a specific product or type of products marketed by the firm, normally do not require consideration from the standpoint of nomenclature.

Line Name.—A line name is a trade name applied to a group

or series of related pharmaceutic preparations having some common distinctive feature in addition to being products of the same firm (e g, tabloid, hypoloid, magmoid, depo—).

Generic Name.—A generic name is an accepted name available for unrestricted use which is unprotected or for which trademark protection has been waived.

Name for Official Article.—A brand name for an official drug will be recognized only if such name actually was in public use before the drug was first admitted in essentially the same form to the *U S Pharmacopeia* or *National Formulary*. The date of such inclusion is understood to be that of the first galley proof of the *U S Pharmacopeia* or of the Bulletin of the National Formulary Committee.

Advantage of Generic Names.—The interests of the patient and physician are served best by adoption of an abbreviated scientific name for general use in prescribing, naming and identifying agents with unwieldy chemical names. The Council believes that the use

generic or official designation of a drug to be displayed adequately and not subordinated unduly to the brand name in labels, labeling and advertising.

Selection of Names

Generic Names.—When practicable, generic names should be coined to conform to scientific usage as advocated by the American

ferent substances and misleading connotations as to identity.

Names of Salts and Esters.—Brand or generic names for simple chemical salts and esters should be coined so as to apply only to the parent drug. (For instance, if the parent substance is given the brand name of Artificialine, and is basic in character, its salt would be designated as Artificialine Chloride, if acid in character, its salt would be designated as Sodium Artificialine or Artificialine Sodium.) Exceptions to this requirement may be permitted when, as judged on the merits of each case, at least one of the following circumstances prevails: (1) the compound significantly alters the action and therapeutic scope of the drug, (2) the usual chemical terminology is too lengthy or unwieldy for practical usage; (3) the introduction of other salts, esters or the free drug is impossible or highly improbable.

Dosage Forms.—Dosage forms of a drug should be identified so

to only one dosage form of a drug if other dosage forms are marketed under another name by the same firm.

Topical Vehicles.—Brand and generic names for separately marketed ointment bases and other topical vehicles are eligible for recognition on the same basis as for single drugs or mixtures, providing such names are not applied also to dosage forms of drugs in which the vehicle is employed. The use of special names for vehicles in designations of drug preparations is likely to multiply confusion in the terminology essential to identify the drug component. Therefore, names for vehicles should be devised to suggest the type of base rather than any particular component.

Mixtures.—Generic and brand names for mixtures containing two or more active ingredients should be coined from the chief components. When one or more of these are present as a salt or ester, they need not comply with the above requirement applied to single agents for distinctive designation of such derivatives.

Subordinate Components.—Components of secondary importance which in some degree modify the therapeutic action of the mixture are preferably named without abbreviation (e.g., Solution Procaine Hydrochloride with Epinephrine 1:100,000). Preparations containing 1 per cent or more of benzyl alcohol or more than 0.5 per cent chlorobutanol must include these ingredients as part of the name.

Use of Numerals and Letters.—The use of numerals or lettered abbreviations or both in whole or part as generic or brand names is considered objectionable except upon adequate scientific justification. Numerals or letters utilized on labels for coding or catalogue identification should be separated clearly from the names of the products.

Names of Biologic Products.—Therapeutically suggestive names are not considered objectionable for serums, vaccines, antitoxins and similar articles.

RULE 6.—Patents and Trademarks.—*The name, number and date of any domestic or foreign patents or trademarks pertaining to an article must be furnished to the Council.*

RULE 7.—Advertising.—*Claims for products shall be limited to those recognized for inclusion in New and Nonofficial Remedies.*

Definition.—For the purpose of this rule, "advertising" is broadly defined to include any and all promotional methods used in the distribution and sale of a product. It, therefore, comprises labels, labeling, mailings and all printed matter; graphic, written or spoken communications including projected pictures, radio, television and other exhibits that pertain to the article. The term, "labeling," is interpreted to mean material which physically accompanies the package in which an article is marketed. Advertising may be separated into two general classes, (1) advertising to the medical and allied professions and (2) advertising to the public.

Responsibility of Firm.—The Council does not undertake to police or censor the advertising of accepted, exempted or re-accepted products, but places upon the firm the responsibility for

making only authorized claims. Claims that are disallowed as a condition of acceptance after consideration of all evidence and statements submitted must be abandoned or revised appropriately before the acceptance is an accomplished fact.

Submission of Advertising—All current and new advertising for submitted, accepted or exempted products should be presented for the information of the Council. The Council cannot edit advertising copy word for word, but rather indicates the general type of revision that may be required. Whenever doubt exists as to rewording or rephrasing, the advice of the Council should be sought in advance of printing or distribution.

References to Medical Literature—References may be used in advertising to published or unpublished reports by permission of the author, provided the name of the investigator, source and date of publication are indicated. Removal from original context of brief quotations to focus attention upon phrases or statements that do not reflect fairly the authors' ultimate conclusions is considered misleading, as well as advertising which contains abstracts of only favorable reports for the product when contrary evidence also is available.

References to New and Nonofficial Remedies—Direct quotations, facsimile reproduction, abstracting or translating into a foreign language of any portion of *New and Nonofficial Remedies* is subject to authorization by the Secretary of the Council.

Seal of Acceptance—The Council permits the use of its official Seal of Acceptance on packages and in advertising only for those

Remedies by the Council on Pharmacy and Chemistry of the American Medical Association."

Variations in the phraseology cited in regard to the Seal must be submitted to the Council and found acceptable before they may be used. When, for any reason, acceptance of an article is rescinded, the Seal must not appear on new labels or advertising; old labels and advertising featuring the Seal must not be in circulation or before the public longer than 6 months subsequent to notification of the revocation. The Seal of Acceptance shall not be used in the promotion of exempt articles, however, exempt drugs may use the designation NNR in advertising.

Advertising of Exempt Drugs—Claims for an exempt product shall not exceed those recognized in the last edition of *New and Nonofficial Remedies* in which the product was described. Exempt products are eligible for advertising in the publications of the American Medical Association, without the seal of acceptance.

Foreign Distribution—When acceptance of an article for in-

clusion in *New and Nonofficial Remedies* is declared in the advertising distributed to foreign countries, advertising claims shall be limited to those recognized for inclusion in *New and Nonofficial Remedies*.

Experimental Uses.—Claims for experimental uses for an accepted product are not permissible on labels, labeling or ordinary advertising. If a firm wishes to issue an informative review of the literature elaborating on all phases of use of an accepted product, experimental uses may be included by presenting an unbiased abstract with appropriate references to all pertinent favorable and unfavorable scientific literature, but without promotional statements, references to Council acceptance, or use of the Seal of Acceptance. Booklets or brochures ordinarily employed for promotional purposes must exclude unestablished information.

Advertising of Unaccepted with Accepted Products.—Accepted or exempt products should not be used for promotion of the sale of unaccepted products. Distribution of separate advertising pieces for accepted and unaccepted products in the same envelope is permissible only when the Seal of Acceptance or a reference to *New and Nonofficial Remedies* is clearly affixed to those enclosures which pertain to accepted products. This requirement does not apply to price lists and catalogs where, at the discretion of the firm, accepted status of a product may be indicated by the Seal of Acceptance or the designation N N R.

Superlative Claims.—Sound therapeutics require avoidance of overenthusiastic claims and inferences for a product as well as avoidance of disparaging statements of recognized standards or competing products. Proper definition, qualification and avoidance of sweeping statements are essential in the preparation of suitable advertising. The use of the personal signature of a physician or the facsimile of such a signature generally is considered objectionable because it may create an exaggerated or misleading impression of value.

Claims for Safety.—Unqualified statements that a product is nontoxic or nonirritating ignore the possibility of varying circumstances which may be encountered in its use. The firm is held responsible for proper qualification of claims so that physicians are not misled in regard to safety.

Permanently Affixed Names.—It is considered desirable to permit physicians to prescribe anonymously when knowledge of the remedy may be detrimental to the patient. Any permanently affixed names or other devices for identifying the article to the public will not be accepted if the Council believes that it would be likely to lead to serious abuse.

Advertising to the Public.—Certain limited classes of products, which in the judgment of the Council may be used with reasonable safety by the public for the palliation of certain symptoms or prevention of infection, are acceptable for inclusion in *New and Nonofficial Remedies*. These include (a) topical disinfectants, antiseptics, fungicidal agents and pediculicides, (b) laxatives, (c) antacids, (d) nonhabituating analgesics, (e) nasal decongestant in-

halers; (f) nonirritant and nonsensitizing antipruritics. In each case the Council believes it is essential to weigh carefully the potential danger, including sensitization, that can result from self-medication and to determine whether the product concerned can be employed safely by the public.

Presentation of Articles

Each presentation should be addressed to the Secretary, Council on Pharmacy and Chemistry, American Medical Association, 535 N Dearborn Street, Chicago 10, Illinois. All letters concerning submitted products should be forwarded in duplicate.

The procedures to be followed in the submission of (1) new articles or brands, (2) new dosage forms of already accepted articles and (3) new firms are outlined below.

New Article or Brand

A Description (See outline below) 3 copies.

B Evidence (laboratory and clinical, see discussion below) Required only of new articles, except when a new brand involves claims for use, administration or dosage not recognized in *New and Nonofficial Remedies*:

1 Reprints or photostats of complete reports 2 copies.

2 Unbiased abstract reviewing all data and giving references or sources of information. 22 copies.

C Labels (container, package, carton) for each submitted dosage form and size, mounted on letter-size paper 22 separate sets.

D Package circular or other enclosures and all proposed or currently distributed promotional literature for all submitted dosages. 22 copies.

E Trade package specimens of the smallest quantity marketed

1 Injectable and other sterile preparations, biologics, antibiotics, topical anti-infectives and disinfectants 6 of each dosage form and size.

2 All other products. 3 of each dosage form and size.

F Bulk sample of the active ingredient as used in manufacture 10 Gm for a new article. If a new brand or a new article is rare or expensive, a lesser amount sufficient to permit duplicate chemical tests for identity, purity and assay may be submitted. When the finished article is supplied in pure, unmixed or undiluted form. A sufficient number of additional trade package specimens to provide an equivalent amount.

Bulk samples of one or more of the components of separately marketed topical vehicles need not accompany a presentation for this type of product. When necessary for analysis of such articles, specified bulk samples of the components will be requested.

Additional Dosage Form or Size

A Description (See outline below) covering completely only items 1, 2 and 3, and the portions of other items (including all

sible side effects or cumulative action in relation to total dosage and duration of administration should be included here. This requirement does not apply to additional dosage forms that do not involve a new route or amended dosage schedule.

6. *Patents and Trademarks.*—Country of origin, number and date assigned and expiration date, of all registered U. S. and foreign patents and trademarks which are applicable to the submitted article. When these are pending, that fact should be stated; the number later assigned in the case of U. S. registration also should be transmitted.

7. *Chemical Data.*—Chemical data whenever applicable to cover the following points:

(a) *General Information.*—Chemical name, empirical and structural formulas and molecular weights of each active ingredient, the name of the supplier or suppliers and a sample of each active ingredient. Where the term "active ingredient" is not strictly applicable, only chemical information is required and should be stated for all components

If the substance is new, references to the chemical literature, especially that containing proof of the structure.

(b) *Physical Properties.* Data on appearance, taste, color, melting point, and on 25°, imp of the c optical r indexes,

Physical properties stated must be those of the grade of ingredient actually used in the manufacture of dosage forms and not properties of highly purified laboratory samples.

(c) *Identity Tests.*—Detailed directions for tests to identify the active ingredient and distinguish it from chemically or therapeutically similar compounds.

... in the presence of the important individual molecules are desirable. ... ribed using some easily measured property, such as melting point, that will indicate a clear chemical distinction between a derivative and its parent compound.

(d) *Purity Tests.*—Tests for the detection of impurities which may have been present in the active ingredient originally or as a result of manufacture.

(e) *Assay.*—Protocols of bio-assay when pertinent should be stated in addition to the following appropriate chemical information.

(1) *Active Ingredient.* Complete instructions or appropriate references to published methods containing complete instructions

for the procedure for assay of each active ingredient. Spectrophotometric methods are preferable to titrimetric methods and there is room to gravimetric methods. Where special equipment is

active ingredient wherever possible.

The accuracy and precision of the methods and the limits of purity that the manufacturer considers satisfactory should be stated.

(f) *Tolerances*—The limits of concentration of the active ingredient, tolerances for the fill of ampuls and bottles, weight of capsules, suppositories, tablets or any dosage forms considered to be acceptable by the manufacturer. Where limits and tolerances exceed those for comparable products given in the official compendia or *N.N.R.*, reasons for the difference should be stated.

- (c) Sterility tests.
- (d) Removal of pyrogens.
- (e) *Pyrogen tests.*

present. See also the section on criteria for the evaluation of certain products for further requirements for topical anti-infectives and disinfectants.

9. *Preparation and Control Procedures.*

(a) General description of method of manufacture. State methods for both active ingredient(s) and dosage forms submitted. Details must be sufficient for the Council to assure itself that

submitted; when these are the same as for previously submitted products that fact should be stated, and when only part of the procedure is the same the points of departure should be covered:

- (1) Precautions to ensure proper identity, strength and purity of the raw materials
- (2) Precautions to preserve sanitary conditions in space allotted to storage of raw materials.

(3) Use of serial numbers to identify each lot of raw materials and the use made of such numbers in subsequent plant operations.

(4) Method of preparation of formula card and manner in which it is used. Specimen blanks of the forms used should be supplied in duplicate.

(5) Manner in which weights and measures of each ingredient are checked when formula is being prepared.

(6) Determination of total weight or volume of each batch at any stage of the manufacturing process subsequent to making up a batch according to the formula card and at what stage and by whom this is done

(7) Methods of maintaining sanitary conditions within the manufacturing plant and avoiding contamination of the drugs with filth, dust and extraneous material

(8) Check of the total number of finished packages produced from a batch of the drug with the theoretical yield.

(9) Precautions to ensure that the proper labels are placed on the drug for a particular lot

(10) The analytic controls used during the various stages of the manufacturing, processing and packaging of the drug, including a detailed description of the collection of samples and the analytic procedures to which they are submitted. If the article is one that is represented as sterile, the same information should be given for sterility controls.

(11) An explanation of the exact significance of control numbers used in the manufacture, processing and packaging of the drug, including any code numbers that may appear on the label of the finished article

(12) Additional procedures designed to prevent contamination and otherwise ensure proper control of the product

(13) Examination of representative samples of each lot of the drug by another laboratory (government or private) prior to distribution. Name of this laboratory.

Note—When any of the procedures described under the headings chemical data, microbiologic data, preparation and control procedures are the methods (unmodified) required or recommended by Federal Law, the *U.S.P.*, *N.F.*, National Institutes of Health, Association of Agricultural Chemists, *New and Nonofficial Remedies* or stated in scientific journals, specific references to such sources may be substituted for the detailed description of these technical procedures.

CRITERIA FOR THE EVALUATION OF CERTAIN PRODUCTS

Certain groups of products present problems that can best be solved when uniform consistency is maintained in the collection of evidence for the preparations in these groups. Accordingly, the Council from time to time proposes criteria to serve as guides in the planning of experiments and the examination of results intended to obtain data to meet the Council rules. So far the

Council has prepared criteria for anti-infective agents, antifungal agents, contraceptive agents, enteric-coated products, mixtures and topical vehicles.

ANTI-INFECTIVES.—For new products (i.e., not in *N.N.R.*) involving claims of antiseptic, bacteriostatic or germicidal effectiveness, or when new claims are advanced, protocols of bacteriologic examination signed by a reputable bacteriologist, and evidence of clinical usefulness which will present studies on toxicity, pharmacology, etc., should be submitted. Where published papers are available, references should be cited.

Criteria for evaluation of skin disinfectants which the Council deems advisable include:

(A) For Antibacterial Agents

1. Phenol coefficients or other *in vitro* tests in the absence and in the presence of serum, using both vegetative bacterial cells and clostridial spores, with suitable recovery mediums containing, if known, neutralizing substances for the disinfectant being tested.

2. Data on germicidal efficiency under conditions simulating actual use by the method of Price (Price, P. B.: *The Bacteriology of Normal Skin. A New Quantitative Test Applied to a Study of the Bacterial Flora and the Disinfectant Action of Mechanical Cleaning*, *J. Infect. Dis.* 63:301 [Nov., Dec.] 1938; *Ethyl Alcohol as a Germicide*, *Arch. Surg.* 38:528 [March] 1939) or, better still, by an extension of the method of Price (Bernstein, L. H. T.: *Standardization of Skin Disinfectants*, *J. Bacteriol.* 43:50 [Jan.] 1942). The complications due to possible effects of the germicide on the skin itself should be taken into consideration (Cromwell, H. W., and Lefler, Ruth: *Evaluation of "Skin Degerming" Agents by a Modification of the Price Method*, *ibid.*, p. 51).

3. Data on germicidal efficiency by an animal method, such for example as suggested by Alice H. Kempf and W. J. Nungester (*An In Vivo Test for the Evaluation of Skin Disinfectants*, *ibid.*, p. 49) or R. W. Sarber (*ibid.*, p. 50).

4. Evidence from animal experiments regarding irritant action on skin and mucosae and regarding systemic toxicity.

5. Critical clinical evidence supporting claims of harmlessness and efficacy.

6. Data on the bacteriostatic activity as distinguished from the germicidal activity of the disinfectant.

(B) For Antifungal Agents.—An extensive discussion of this subject appears in *The Journal* as a Council report (*J.A.M.A.* 128:805-811 [July 14], 1945). For guidance the data suggested may be divided into three parts: (1) laboratory tests of the fungicide, (2) clinical tests and (3) toxicity tests, and obtained as follows:

1. *In Vitro Tests of Fungicide.*—The phenol coefficient test for disinfectants and antiseptics as modified by the American Public Health Association subcommittee should be used. For convenience, this is resubmitted, but in synoptic form. A detailed report is published in the *American Journal of Public Health* for 1945 of

These examinations should be regarded as only supplementary to the clinical findings; many cases of valid dermatophytosis fail to yield confirmatory laboratory evidence, but the laboratory examinations may clarify doubtful clinical cases, and a knowledge of the identity of the species may be valuable when analyzing therapeutic results later. Thus, a fungicide eventually might be discovered which was efficacious against *Trichophyton purpureum* or other fungus but not against other species, and vice versa.

(d) Number and Duration of Treatments: As a working rule, applications should be made at night and in the morning for 2 weeks. A final or subfinal examination should be made at the end of 4 weeks.

(e) Faithfulness of Patient to Treatment. The investigator should appraise the human type of each patient before admitting him to the test series and have no hesitation in rejecting the unpromising ones. Lapses in treatment demand that the patient be removed from the series and is one more reason for securing a larger number of patients at the beginning of the work than will be employed in the final evaluation.

(f) Privacy on Part of Patients. Patients should be requested not to discuss their treatment programs with other patients; they may influence one another's opinions. For obvious reasons, clinical tests should not be conducted on patients who are employed in plants that have a gainful interest in the fungicide being tested.

(g) Local Irritant Effect of Fungicide. This should be substantially nil, considering the number of fairly effective therapeutic agents now existent that are free from irritant effects. Certainly, the development of any reactions that are at all severe should at once condemn the agent.

(h) Sensitization to the Fungicide. This factor enters into and is inquired for routinely in tests of local applications in general. In the case of dermatophytosis it will take care of itself largely during the clinical tests of fungicidal value, where the applications are "interrupted" in the natural course of events. The appearance of flare-ups shortly after the eighth day of treatment should be watched for. If they do appear, a special set of tests for sensitization must be made.

(i) Toxic Systemic Effects. These should not play a role of importance in the evaluation of a fungicide.

amount that can be absorbed from skin. Such animal tests can follow the plans already developed for bacterial disinfectants and antiseptics. The Bureau of Ships Circular 51D6 (Int.), Dec. 15, 1942, page 4, paragraph F-2d may be followed in this connection.

(j) Readings of Results of Treatment. These should be made without any knowledge of the identity of the patient or of the treatment that has been employed; an assistant should have removed, if possible, any traces of telltale fungicide that may remain. Only in this way can the factor of bias be completely

removed and a fair, impartial evaluation secured. If at all possible, the readings should be made by a disinterested person.

(k) *Mycologic Checks on Therapeutic Results:* These will have value only of a kind supplementary to the clinical opinions because of the increased difficulty in laboratory demonstration of fungi in treated lesions. At the conclusion of therapy they should be made on the "cured" and "nearly cured" patients and again on the cured patients 4 weeks after cure. Positive results will have larger definitive value because they will indicate that the fungicide has not killed. With negative results there is a possibility that fungi are still present but not demonstrable. In any event this mycologic check should be performed so that the data may be available when making final evaluation. The competence of the examiner in recognition of fungi is of paramount importance.

(l) *Grading of Results:* "Cured," "almost cured," "improved," "stationary," and "worse" are suggested, but each worker is at liberty to select any system that suits his purposes; but he should be clear beforehand for his own guidance as to the criteria for grading, from this there should be no deviation later. A subdivision like this into five grades reduces the number of cases available for subsequent statistical purposes and illustrates once again the necessity for numerous patients to begin with. Opinions of patients as to results should not be depended on too much; in cases of doubt they should be discounted. Patients commonly regard themselves as cured when itching ceases. It will be conducive to accuracy if the physician has an assistant who will independently grade the results, the final grading being decided in consultation on the spot.

3. *Toxicity Tests.*—These should be performed depending on the individual circumstances surrounding the chemical concerned. Where there is a hazard the Bureau of Ships circular entitled "Disinfectant, Germicide and Fungicide," page 4, paragraph F-2d may be followed. Ten healthy adult albino rats weighing between 150 and 250 Gm. should be employed, none pregnant. They should be fed as usual. Three-tenths cc. of the fungicide (standard strength) per kilogram of body weight should be slowly inserted obliquely into the peritoneal cavity. The animal then should be given the usual food and water and observed for untoward effects for 72 hours.

CHEMICAL CONTRACEPTIVE AGENTS.—For guidance in reviewing contraceptive products, the Council on Pharmacy and Chemistry has proposed the following criteria.

1. The use of the word "contraceptive" need not be limited to materials that will prevent conception on every occasion of use.

2. Evidence shall be furnished that use of the material decreases the incidence of pregnancy. This evidence may be secured in connection with occlusive devices unless the manufacturer's advertising is directed chiefly toward the use of the jelly or cream without such devices. It is desirable that each case reported should be observed for at least 12 months, and that the minimum of 75 patient-years of experience should be reported. (Thus 50 patients for 18 months or 25 patients each followed for 3 years would be the equivalent

of 75 patients for 12 months.) If cases are excluded from the series on the basis of their being irregular users, the number excluded and the nature of the evidence justifying their exclusion should be stated.

3. Evidence shall be submitted that 100 or more couples have used the material on six or more occasions without irritation or injury.

4. Evidence is desirable that 12 or more women have received vaginal applications of the recommended dosage on 21 successive days without subjective irritation or injury and without evidence of physical damage shown on speculum examination by a physician with special experience in this field. Thus, inspection of the vagina at least once a week should be done as a protection to the patient in case the jelly proves to be irritating.

5. The quantitative formula from which the contraceptive mixture is prepared shall seem to the Advisory Committee to be safe and, presumably, effective.

6. The consistency shall be satisfactory to the committee. It shall not show separation into more liquid and more solid portions visible to the naked eye.

7. Evidence shall be submitted that the consistency is not substantially changed after storage for 12 months at 27°.

8. The consistency shall be reasonably uniform from batch to batch

9. The spermicidal time of the contraceptive material as measured by the method of Brown and Gamble (*JAMA*. 148:50 [Jan. 5] 1952) with proportions of material, isotonic solution of sodium chloride and semen of 1:4.5 shall be 30 minutes or less as measured by the average of four or more tests.

10 The use of jellies or creams suggested by the manufacturer need not be limited to use in conjunction with an occlusive device.

11. If a syringe applicator or nozzle is furnished for use in connection with the jelly or cream, it shall be sufficiently translucent to permit the detection of air that might lead to inadequate dosage.

12. If a perfume is used, a quantitative statement of ingredients is required.

such drugs as diethylstilbestrol or digitalis acceptable because they do not meet the above requirements and are not superior in any way to plain dosage forms.

MIXTURES.—The effects of drugs are intrinsically so complex that it is generally advisable to administer them singly. However, concomitant administration of two or more medicinal agents may be indicated if the particular drugs assist each other to produce an effect that no one of them could effect alone, or if this procedure significantly reduces toxic or side effects. Ordinarily, it is wiser to administer them separately in order that the dosage and frequency of administration of the individual drugs may be varied in accordance with the patient's requirements.

There may be advantages in prescribing mixtures "ready-made" when the administration of the components in the same fixed ratio can be justified, as with certain vitamin preparations; when they are always given at the same time, as with procaine hydrochloride and epinephrine injections; and when extemporaneous compounding is too complicated.

The Council, therefore, accepts mixtures only if they fulfill the following conditions:

1. (a) The active ingredients together accomplish significant therapeutic results that could not be expected from one ingredient alone, and/or

- (b) Use of the ingredients together diminishes the toxic or side actions.

2. The particular ratio of the active ingredients can be justified so as to avoid unnecessary multiplication of ratios for practically equivalent mixtures.

3. The ingredients cannot be conveniently compounded extemporaneously.

Decisions of General Interest

In order to aid manufacturers and distributors of medicinal articles that conform to the requirements of the Council's rules, certain statements which have been adopted by the Council are presented herewith.

The Use of Numbers and Letters in Names

Some time ago the Council adopted the following statement expressing its attitude and requirements with regard to the use of numeral and alphabetical designations in the names of pharmaceutical products:

"Since the use of numeral or alphabetical designations in connection with drug names tends to take the emphasis away from the name and to displace the name, thus leading to confusion, the Council will not recognize the name of a drug in which the numeral or letter is an integral part of the name, except in special cases where the use of a numeral or letter seems desirable

in advertising, unless the numeral or letter is clearly separated from and subordinated to the name by type and if feasible by position. This rule does not apply to price lists and catalogs."

The rule has been interpreted to apply also to alphabetical and numerical combinations which are sometimes used as trademarks.

that would tend to make them a part of the name or a substitute for it, in the minds of the prescriber or the public. It countenances their use only for the convenience of the wholesaler.

To aid manufacturers and distributors in the preparation of labels which meet the requirements of this rule, the Council offers the following examples of acceptable and unacceptable number set-ups on labels:

Acceptable

ELIXIR BROMIDES
COMPOUND
No. 42

Unacceptable

ELIXIR No. 42 BROMIDES
COMPOUND

Acceptable

100 cc.	List No. 88
SYRUP	
EPHEDRINE COMPOUND	

Unacceptable

SYRUP
EPHEDRINE COMPOUND
No. 88

(The typography of the numbers in the "acceptable" labels should be subordinate to that of the name-itself.)

These examples do not cover all types of labels but they should serve to give some idea of what the Council is attempting to accomplish in the way of compliance with its rule prohibiting the use of numbers as integral parts of names.

These principles apply also to collateral advertising. No objection will be made, however, to a statement in the concluding paragraph of the text of an advertisement or circular to the effect that the product advertised is listed in their catalog as

"(Name of product) No. "

Spelling of Basic Products Having an "Amine" Group

The Council has expressed the opinion that the names of products that are basic and contain an "amine" group should end with the letter "e" and that the names of these products also should contain, if indicated, the additional term "hydrochloride" or "sulfate." Scientific nomenclature, in general, indicates a product with a name ending in "in" alone to be glucosidal in nature, whereas the ending "ine" would indicate that the compound is of a basic character. This style of nomenclature conforms with that adopted by scientific societies such as the United States Pharmacopeial Convention, the American Chemical Society and the American Society of Biological Chemists. For the past few years the Council has required adoption of this style of nomenclature for new products submitted to it, and, for the sake of uniformity it urges adoption of the final "e," where needed, for old products as well. The Council asked all firms to co-operate in adopting this style of nomenclature and revise the names of their products that are basic and contain an "amine" group to include the final "e."

Uniform Spelling of "Ampul" and "Ampuls"

The Council voted to adopt the uniform spelling "ampul" and "ampuls" whenever reference is made in its publications to this form of container. This spelling will apply in all instances except the names of accepted preparations in the title of which the firm uses a different spelling. In such instances the Council has requested that an effort be made to obtain conformity with the preferred spelling but failure to effect the change will not be held as a bar to Council acceptance of a drug.

Mineral Waters

The Council considers that artificial mineral waters are non-essential modifications of natural waters, and that natural mineral waters are only one feature prescribed by spas and health resorts. Mineral waters bottled for individual use are not eligible for acceptance, since there is no convincing evidence of the validity of the many therapeutic claims which are made for these preparations.

Nasal Inhalant Preparations Containing Petrolatum

For several years brands of nasal inhalant preparations marketed in oily or ointment vehicles, consisting wholly or in part of petrolatum (principally liquid petrolatum) were included in *New and Nonofficial Remedies*. The Council reviewed the status of such preparations and is of the opinion that the repeated use of nasal inhalant preparations containing a vehicle of liquid petrolatum may lead to undesirable effects and is especially dangerous from the standpoint of lipid pneumonia, furthermore, that inhalant preparations containing petrolatum offer no indispensable advantages over similar preparations containing vehicles of vegetable oils. The Council, therefore, omitted from *N.N.R.* all brands of inhalant nasal preparations containing petrolatum because of the danger of lipid pneumonia from repeated intranasal use and the fact that other safer vehicles for inhalant preparations are available. The Council has retained in *N.N.R.* only those oily inhalants that do not contain petrolatum, pending the development of more positive evidence concerning the irritative properties of other types of oils.

Solutions and Suspensions for Ophthalmic Use

Before accepting any solution or suspension for ophthalmic use the Council requires that the manufacturer submit protocols to show that adequate tests for sterility are made before release of any batch of the finished product.

Penicillin and Sulfonamide Preparations for Topical Applications and Dermatologic Preparations of Antihistamine Drugs

The Council has voted to omit from *New and Nonofficial Remedies* all penicillin and sulfonamide preparations (troches, ointments and ophthalmic ointments) designed for topical application and dermatologic preparations (creams and ointments) of antihistamine drugs because their therapeutic value appears to be outweighed by the high incidence of sensitivity reactions attending such use of these drugs. The Council, therefore, no longer considers such products for inclusion in *N.N.R.*

10 Per Cent Solutions of Sodium Morrhuate Not Acceptable

For some time the Council recognized the use of solutions of sodium morrhuate as a sclerosing agent for the injection treatment of varicose veins, and both 5 per cent and 10 per cent solutions in combination with a local anesthetic were accepted for inclusion in *New and Nonofficial Remedies*. After due consideration of the available information, the Council voted to omit all accepted brands of the 10 per cent solution of sodium morrhuate because of its questionable utility and because serious accidents have followed the use of the stronger solution in the treatment of varicose veins.

The Council authorized a revision of *N.N.R.* to include a recommendation for the use of a preliminary test dose as a precaution against untoward reactions with 5 per cent solutions.

Avoidance of "Split Titles" on Labels

Several instances have arisen in which the Council has been asked to give an opinion concerning the formulation of titles on labels. The following forms are submitted as examples:

SYNTHETIN
(Reg. U. S. Patent Office)
HYDROCHLORIDE

SYNTHETIN
Brand of—(generic name)
HYDROCHLORIDE

The Council ruled that the splitting of names was objectionable, in that it might lead to confusion on the part of physicians and pharmacists, and, therefore, should be avoided. It was recommended that the labels given above be revised as follows:

SYNTHETIN HYDROCHLORIDE
(Synthetin is registered in the U. S. Patent Office)

SYNTHETIN* HYDROCHLORIDE
*BRAND OF—(GENERIC OR CHEMICAL NAME)

Therapeutic Agents Derived from Animal Sources for Parenteral Use

The Council has considered the reasonable possibility that the use of therapeutic agents derived from animal sources may precipitate allergic reactions in individuals who have an allergic susceptibility to certain animals. Such allergic reactions would be most likely to occur in the use of noncrystalline preparations for parenteral use. Therefore, the Council recommended that the source of animal products be declared on the label for accepted brands of noncrystalline products for parenteral injection and products for local application on freshly denuded surfaces, these to include preparations of liver extract, parathyroid solution and thromboplastic

substances This also may be applied in the future to other preparations where evidence indicates the possibility of allergic reaction.

Variations in Labeled Content of Accepted Preparations

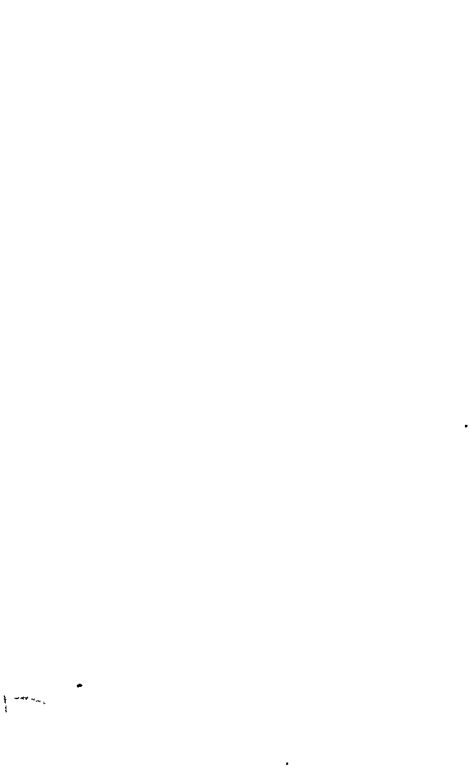
Preparations varying beyond 5 per cent, plus or minus, of labeled content will be accepted only if such variation may be especially justified.

Definition of "Label" and "Labeling"

The Council voted to adopt the definition of the Federal Food, Drug and Cosmetic Act of "label" and "labeling," which is given as follows:

The term "label" means a display of written, printed or graphic matter upon the immediate container of any article

The term "labeling" means all labels and other written, printed or graphic matter upon any article or any of the containers or wrappers accompanying such article.



THE COUNCIL AND OFFICIAL AGENCIES

The Relation of the Council to Other Bodies and to Governmental Agencies Regulating Drug Products and Their Advertising

There are several official and quasi-official bodies concerned with products. Some of these are closely connected with the work of the Council and may be

understood and their spheres of influence as they pertain to therapeutic agents defined, the following brief descriptions of their organizations and duties are given:

The Food and Drug Administration: This agency is part of the United States Department of Health, Education and Welfare and is charged with the enforcement of the Federal Food, Drug and Cosmetic Act, the Caustic Poison Act and several other statutes. The Food and Drug Administration is directed by the Commissioner of Food and Drugs and has several district offices in New

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York. Five offices and special laboratories are located in Washington.

The Federal Food, Drug and Cosmetic Act regulates the labeling of drug products, but its authority does not extend to advertising. Seizure of offending goods, or criminal prosecution of responsible firms or persons in federal courts are among the methods used to enforce the provisions of the Act. In addition, repeated violations may be enjoined by the courts.

Violations may consist of either adulteration or misbranding or

name of each active ingredient and the quantities of certain specified ingredients, adequate directions for use unless exempted by regulation in which case the label must bear the statement "Caution, to be dispensed only by or on the prescription of a physician," and adequate warnings against possible misuse. The Act further prohibits the distribution of drugs that may be dangerous to health under the conditions of use prescribed or recommended in the labeling or of drugs which are deceptively packaged. New drugs may not be introduced into interstate commerce unless an application has been permitted to become effective. Such an application must show by adequate scientific evidence that the drug is safe for use under the conditions proposed for its use.

Certain drugs, namely, insulin, penicillin and streptomycin, are subject to special control. Samples of each batch of these drugs are examined by the Food and Drug Administration for compliance with standards set forth in regulations issued by the Administration. Each batch must be certified as complying with these standards before the batch may be distributed. Such batches of these drugs are referred to as "certified drugs."

The Federal Trade Commission: The Federal Trade Commission is an independent agency of the Federal Government directly responsible to the President. The Commission administers several laws, the principal one being the Federal Commission Act. The principal provisions of this act have to do with the regulation of trade practices.

The Federal Trade Commission is composed of five members, appointed by the President. Not more than three of the members may be of any one political party, and the members serve for 7-year terms. The work of the Commission is organized under divisions, and that having to do with drug products is known as the Medical Advisory Division.

The principal power of the Federal Trade Commission with respect to drugs lies in Section 15 of the Federal Trade Commission Act which was amended by the Wheeler-Lea Act in 1938 giving the Commission control over the advertising of Foods, Drugs and Cosmetics. Although the Commission has broad power to prevent the dissemination of false or misleading advertising to the general public, this power is circumscribed with respect to advertisements directed to the medical profession. The Act states "No advertisement of a drug shall be deemed to be false if it is disseminated only to members of the medical profession, contains no false representations of a material fact, and includes, or is accompanied in each instance by truthful disclosure of, the formula showing quantitatively each ingredient of such drug."

The enforcement of the Federal Trade Commission Act rests with the Commission. Trial of cases involved in violations is held

instances, controversies may be settled by stipulations between the Commission and respondents.

The United States Public Health Service: Among the many functions of the United States Public Health Service is the regulation of biologic products. The Division of Biologics Control of the National Institutes of Health administers that part of the Public Health Service Act of 1944 which incorporates the former Viruses, Serums, Toxins and Analogous Products Act.

The control exercised by the Public Health Service Act extends only to biologic products which are defined as "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man." By further definition, the term "biologic products" is extended to cover trivalent arsenical compounds. Pentavalent arsenical compounds are controlled under the Federal Food, Drug, and Cosmetic Act by administrative agreement between the Public Health Service and the Food and Drug Administration.

The control exercised by the Public Health Service over biologic products is through the inspection and licensing of establishments producing such products and by the examination and licensing of the products themselves. It is illegal, therefore, to produce any biologic product in an establishment that has not been duly licensed by the Public Health Service or to ship in interstate commerce any biologic product for which a license has not been issued and which is not effective at the time of shipment.

In order for a biologic product to be licensed under the provisions of the Public Health Service Act, it must meet the standards prescribed by the Division of Biologics Control of the National Institutes of Health, and each batch must be tested for compliance with these standards. The labels of these products must bear the proper name of the product, the name, address and license number of the manufacturer, the lot number and the expiration date. Under certain conditions, and in the case of certain products, additional information may be required to appear on the label.

The United States Treasury Department: The Bureau of Narcotics of the United States Treasury Department administers the Harrison Narcotic Act. This Act is part of the Internal Revenue Code and is primarily a taxing measure. The Act provides for the payment of certain taxes and the affixing of revenue stamps to lots of narcotic drugs.

Under the Harrison Narcotic Act, opium, cocoa leaves or any derivatives thereof or marihuana or any derivative thereof is defined as being subject to the Act. Furthermore, by an amendment passed in 1946, the President may proclaim a drug as addiction-forming or addiction-sustaining upon a finding by the Secretary of the Treasury after due notice and an opportunity for a public hearing, and bring such a drug within the purview of the Harrison Narcotic Act. Under this provision, the drug Methadon (amidone) was proclaimed subject to the Act on July 31, 1947.

Although a tax measure, the Harrison Narcotic Act prescribes rigid controls over the transportation and distribution of narcotic drugs. Only physicians duly licensed under this Act may prescribe

these drugs, and the form of such prescriptions and their handling is set forth in considerable detail.

The Post Office Department: The Fraud section of the post office under the direction of the Solicitor enforces the law pertaining to the fraudulent use of the mails. The use of the United States mails is a privilege and not a right and may be denied to those who use it for the purpose of defrauding the public. Therefore, the solicitation of customers and the shipping via the mails of drugs for which fraudulent claims are made may be the basis for the issuance of a "fraud order" and the suspension of all mail service to the guilty party. Determination of the guilt is made by the Solicitor after a hearing before him in which the facts are presented. Repeated violations or efforts to avoid compliance with such fraud orders may lead to criminal prosecution in the Federal Courts.

The United States Pharmacopoeial Convention: Under the General Committee on Revision, the United States Pharmacopoeial Convention issues at 5-year intervals (formerly 10-year intervals) the *United States Pharmacopeia*. The United States Pharmacopoeial Convention is a private body composed of representatives from medical schools, pharmacy schools, state medical associations, state pharmaceutical associations, the American Medical Association, the American Pharmaceutical Association, the American Chemical Society and many other scientific and trade associations and also various interested federal bureaus and departments.

Under authority of the Federal Food, Drug, and Cosmetic Act, the *United States Pharmacopeia* is an official standard for the products described therein. Products are accepted for inclusion in the *Pharmacopeia* by the Committee on Revision on the basis of demonstrated therapeutic value or pharmaceutical necessity.

The American Pharmaceutical Association: The *National Formulary* is issued by the Committee on the National Formulary elected by the Council of the American Pharmaceutical Association. Admission of products to the *National Formulary* is based upon therapeutic value as well as upon the extent of use of the drug and the apparent need for official standards of certain drugs not necessarily widely used.

Under authority of the Federal Food, Drug and Cosmetic Act, the *National Formulary* is an official compendium, and drugs described therein must meet the standards set forth in that publication.

THE METRIC SYSTEM

Formerly almost every country had its own system of weights and measures, a practice that resulted in much confusion. The one system that is used almost universally and exclusively in the exact sciences is the metric system, which is based on the decimal system and has for its units the meter and the gram.

The Council on Pharmacy and Chemistry has voted to use exclusively the metric system in any publication for which it has sole

responsibility. For this reason a table of equivalents will be provided in each book for those who are familiar only with the apothecary system.

Table of Metric Doses with Approximate Apothecary Equivalents

The approximate dose equivalents in the following table represent the quantities that would be prescribed, under identical conditions, by physicians trained, respectively, in the metric or in the apothecary system of weights and measures.

When prepared dosage forms such as tablets, capsules, pills, etc., are prescribed in the metric system, the pharmacist may dispense the corresponding approximate equivalent in the apothecary system, and vice versa. However, this does not authorize the alternative use of the approximate dose equivalents given below for specific quantities on a prescription that requires compounding, nor in converting a pharmaceutical formula from one system of weights or measures to the other system, for such purposes exact equivalents must be used (see *U.S.P. XIV* Table, page 1019).

<i>Weights</i>		<i>Weights</i>	
Metric	Approximate Apothecary Equivalents	Metric	Approximate Apothecary Equivalents
30 Gm. = 1 ounce		40 mg. = $\frac{3}{4}$ grain	
15 Gm. = 4 drachms		30 mg. = $\frac{1}{2}$ grain	
10 Gm. = $2\frac{1}{2}$ drachms		25 mg. = $\frac{3}{8}$ grain	
7.5 Gm. = 2 drachms		20 mg. = $\frac{1}{3}$ grain	
6 Gm. = 90 grains		15 mg. = $\frac{1}{4}$ grain	
5 Gm. = 75 grains		12 mg. = $\frac{1}{5}$ grain	
4 Gm. = 60 grains (1 drachm)		10 mg. = $\frac{1}{6}$ grain	
3 Gm. = 45 grains		8 mg. = $\frac{1}{8}$ grain	
2 Gm. = 30 grains ($\frac{1}{2}$ drachm)		6 mg. = $\frac{1}{10}$ grain	
1.5 Gm. = 22 grains		5 mg. = $\frac{1}{12}$ grain	
1 Gm. = 15 grains		4 mg. = $\frac{1}{15}$ grain	
0.75 Gm. = 12 grains		3 mg. = $\frac{1}{20}$ grain	
0.6 Gm. = 10 grains		2 mg. = $\frac{1}{50}$ grain	
0.5 Gm. = $7\frac{1}{2}$ grains		1.5 mg. = $\frac{1}{40}$ grain	
0.45 Gm. = 7 grains		1.2 mg. = $\frac{1}{50}$ grain	
0.4 Gm. = 6 grains		1 mg. = $\frac{1}{60}$ grain	
0.3 Gm. = 5 grains		0.8 mg. = $\frac{1}{80}$ grain	
0.25 Gm. = 4 grains		0.6 mg. = $\frac{1}{100}$ grain	
0.2 Gm. = 3 grains		0.5 mg. = $\frac{1}{120}$ grain	
0.15 Gm. = $2\frac{1}{2}$ grains		0.4 mg. = $\frac{1}{150}$ grain	
0.12 Gm. = 2 grains		0.3 mg. = $\frac{1}{200}$ grain	
0.1 Gm. = $1\frac{1}{2}$ grains		0.25 mg. = $\frac{1}{250}$ grain	
75 mg. = $1\frac{1}{4}$ grains		0.2 mg. = $\frac{1}{300}$ grain	
60 mg. = 1 grain		0.15 mg. = $\frac{1}{400}$ grain	
50 mg. = $\frac{3}{4}$ grain		0.1 mg. = $\frac{1}{600}$ grain	

Table of Metric Doses with Approximate Apothecary Equivalents—Continued

<i>Liquid Measures</i>		<i>Liquid Measures</i>	
Metric	Approximate Apothecary Equivalents	Metric	Approximate Apothecary Equivalents
1000 cc.	= 1 quart	3 cc.	= 45 minims
750 cc.	= 1½ pints	2 cc.	= 30 minims
500 cc.	= 1 pint	1 cc.	= 15 minims
250 cc.	= 8 fl ounces	0.75 cc.	= 12 minims
200 cc.	= 7 fl ounces	0.6 cc.	= 10 minims
100 cc.	= 3½ fl ounces	0.5 cc.	= 8 minims
50 cc.	= 1¾ fl ounces	0.3 cc.	= 5 minims
30 cc.	= 1 fl ounce	0.25 cc.	= 4 minims
15 cc.	= ½ fl ounce (4 fl drachms)	0.2 cc.	= 3 minims
10 cc.	= 2½ fl drachms	0.1 cc.	= 1½ minims
8 cc.	= 2 fl drachms	0.06 cc.	= 1 minim
5 cc.	= 75 minims (1¼ fl. drachms)	0.05 cc.	= ¾ minim
4 cc.	= 1 fl. drachm	0.03 cc.	= ½ minim

1 Troy or Apothecary ounce = 31.1 grams (Gm)

1 Avoirdupois ounce = 28.35 grams (Gm)

1 Avoirdupois pound = 453.6 grams (Gm)

NOTE—A cubic centimeter (cc) is the approximate equivalent of a milliliter (ml.).

I Agents Used in Allergy

This chapter deals with prophylactic and therapeutic agents that are capable of controlling allergic phenomena. Only the histamine-antagonizing compounds are described here. Food, epidermal and other allergenic extracts are exempted from inclusion in *New and Nonofficial Remedies*. For reference to such products formerly included, see *N.N.R. 1950*. Sympathomimetic agents of value for this purpose are described in the chapter on autonomic drugs, and cortisone and related compounds are described in the chapter on hormones and synthetic substitutes, however, their use in the treatment of allergy will be discussed briefly in this chapter.

Agents used in the prevention and treatment of allergic manifestations may exert their action in one of several ways. These are chiefly by producing sedation, vasoconstriction, bronchial relaxation, and liquefaction of bronchial secretions and by competition with histamine, by desensitization and by modification of tissue reactivity.

Vasoconstrictors.—Among the most effective drugs in the symptomatic treatment of allergy are the vasoconstrictors. These include such drugs as epinephrine, ephedrine, racephedrine, phenylpropanolamine, naphazoline and amphetamine. Their action is primarily a *constriction of the blood vessels and a diminution of further exudation of fluids in the tissue* responsible for the particular allergic symptoms. Some of these vasoconstrictors are also good bronchodilators. The most potent of these drugs is epi-

anaphylactic shock and angioneurotic edema of the larynx. Since

for the relief of asthma. It has the disadvantage, however, of causing a local vasoconstricting action in the throat and, subsequently, possible harmful effect on local tissue. In recent years this drug has been supplanted largely by isopropyl epinephrine for inhalation therapy.

Sympathomimetics.—Ephedrine is the most useful of the sympathomimetic drugs given orally. Its effect is of several hours duration but is not as intense as that of epinephrine. It tends

to produce the same side actions as epinephrine but in a more moderate degree. In men who might have prostatic hypertrophy it may produce difficulty in urination. Racephedrine has a less potent action than ephedrine and also lesser side actions. Phenylpropanolamine is still less potent than either of the above but can be used as a substitute when the ephedrine compounds are objectionable. These drugs, as well as naphazoline, amphetamine and others, have been employed topically, particularly in the nose, for their decongestive effect. They are useful in sinus infections for promoting drainage, in clearing the nasal passages in the acute cold and occasionally in allergy for an acute blocking of the nasal passages. They should not be used, however, in persistent nasal allergy or in other forms of chronic rhinitis. In such conditions the almost inevitable effect is to produce a rebound action of the mucosa, that is, an increased congestion after the constricting effect wears off, thus promoting a vicious cycle. In such cases it is much better to substitute the antihistamines or other oral drugs.

Bronchodilators.—Among the bronchodilator drugs free from vasoconstrictor action, aminophylline has been one of the most useful. It is most effective when administered intravenously, less effective rectally and least effective orally. Intravenously it will often supplement the action of epinephrine or even be effective when epinephrine has failed. In acute anaphylactic shock it should be given to supplement epinephrine therapy. Its use in conditions other than asthma or anaphylactic shock is questionable. Aminophylline may cause nervousness from cerebral stimulation. It is also a gastric irritant. Other xanthine derivatives also may be useful as bronchodilators. Other bronchodilators such as atropine or stramonium are rarely useful, probably since the effective dose cannot be achieved because of toxic effects. However, inhalation of the smoke of ignited, dried stramonium combined with potassium nitrate may produce effective relief of bronchospasm. In recent years isopropyl epinephrine has been used extensively in the relief of asthma. It is administered chiefly by inhalation of a spray or dust and at times by sublingual pellets. Its greatest advantage is that it has no pressor effect, although it does produce cardiac stimulation and cerebral excitation.

Iodides.—In addition to bronchospasm and edema of the mucosa, another mechanism in asthma adding to the bronchial obstruction is the hypersecretion of tenacious mucus by the bronchial glands. The iodides constitute the most effective remedy for this phase of asthma. The action of the iodides is to stimulate the bronchial glands to secrete a thin discharge, thus alleviating the plugging effect. Iodides usually are given orally in solution in the form of the potassium salt. If gastric irritation is produced, enteric-coated tablets may be employed. Although true allergic reactions to iodides may occur (consisting of fever and serious drug eruptions), most side effects are not allergic. They are of the nature of toxic reactions that would occur in virtually anyone who received large doses. In the approximate order of frequency these reactions are gastric irritation, acneiform eruptions, rhinorrhea, nasal blocking, sinus congestion, edema of the eyelids and swelling

of the salivary glands. The use of iodides for asthma in the presence of pulmonary tuberculosis has been regarded as dangerous although the evidence for this is not conclusive. Experience indicates that there is very little possibility of such a hazard if anti-tuberculous drugs are employed concurrently. When iodides are not tolerated, expectorants such as ipecac, ammonium chloride or apomorphine may be of some help.

Sedatives.—Sedation in allergic disease may be employed for several purposes: to obtain rest, to allay apprehension and to counteract the stimulating effects of epinephrine, ephedrine and aminophylline. The possibility of cutaneous allergy, such as morbilliform rashes and fixed drug eruptions, from barbiturates must be considered. For sedation, particularly in asthma, chloral hydrate is more effective. Opiates generally are contraindicated in itching dermatoses and in asthma. Morphine or codeine may increase pruritus. Although morphine may allay apprehension in asthma, its depressing effect on cough and respiration may make the asthma worse. Experiments with animals indicate further that morphine is a bronchoconstrictor. Codeine and meperidine are less objectionable, but their desirability usually is outweighed by the hazards of their use.

Hormones.—Corticotropin, cortisone and hydrocortisone have assumed an active role in the treatment of some of the allergic diseases. Their effect is to modify the reacting tissue so that it responds less to the antigen-antibody reaction. Corticotropin must be given intramuscularly and, at times, intravenously. Cortisone may be administered orally, in addition to intramuscularly. Recently the free alcohol of cortisone also has been administered intravenously. These hormones have their chief use in treating temporary severe allergic manifestations such as acute status asthmaticus, very severe and short-term seasonal asthma and hay fever and severe drug and serum reactions of the delayed serum sickness type. Corticotropin and cortisone also have been used for protracted periods, particularly in cases of chronic asthma. The doses, methods of administration, onset of relief and precautions for use are about the same as described in the chapter on hormones and synthetic substitutes. It should be noted especially that the initial and maintenance doses of cortisone or corticotropin may have to be higher in allergic conditions than in other conditions. Withdrawal of cortisone must be gradual to avoid serious relapses. These drugs should not be used in place of simple palliative therapy, such as antihistamines, epinephrine or ephedrine, nor employed as a short cut for diagnosis of the allergy nor as a substitute for desensitization. Neither are they effective in anaphylactic reactions. These hormones have an important place in the treatment of allergy, but unless used with reason and caution they can result

in therapy more recently.
ve to cortisone when given
some that the dose required
ever, in ointments of 1 to
has proved to be highly

effective in localized cutaneous lesions, such as atopic dermatitis, contact dermatitis and insect bites.

Allergenic Extracts.—Materials suspected of causing allergic manifestations are commonly used either for diagnostic or immunizing procedures. These consist mainly of extracts of air-borne pollens and molds, dandruffs of animals, house dust, some miscellaneous inhalants, foods and contact substances. All of the antigens (except the contactants) are extracted with an aqueous medium, usually with either saline, glycerin, dextrose or Coca's solution added, and an antiseptic. These antigenic extracts are employed diagnostically, either by scratch or intradermal technic and, at times, by mucous membrane testing. On the skin a diagnostic reaction consists of an urticarial wheal occurring in a few minutes. A positive reaction must be checked clinically before it can be accepted as a cause of the patient's complaint. Often the offending agent, such as feathers, dogs or food, can be removed. If this cannot be done for certain inhalants, such as pollen, mold and dust, desensitization therapy is advisable. It

beginning with
desensitization

patients, but treatment usually must be continued over a period of one to several years. In many such instances, remissions of one to several years often occur after discontinuance of therapy. Desensitization is the only therapeutic method in allergy thus far which offers the hope of lasting results.

In contact dermatitis, diagnostic tests are made by the patch methods with raw materials, such as plants and textiles, or with solutions or extracts. In plants, such as poison ivy, primrose and ragweed, it is the ether-soluble, not the water-soluble, fraction that is responsible for the dermatitis. The patch test consists of permitting the material to stay on the skin for 24 to 48 hours. A positive test consists of redness, swelling and, frequently, vesiculation. As with the scratch and intradermal tests, the patch test must be used cautiously to avoid systemic reactions.

HISTAMINE-ANTAGONIZING AGENTS

Actions.—The knowledge that histamine is released in the development of compounds must be re-examined. Specific methods in the general attributes of this discussed here briefly, the monographs on each drug

These drugs, orally and intravenously, prevent bronchospasm and wheezing on histamine wheal on histamine strip of the guinea pig in vitro. They prevent experimental histamine asthma in man and hypotension due to histamine in the cat and dog. Some actions of histamine, such as the stimulation of

salivation and gastric secretion, are not inhibited by the antihistaminic drugs. These compounds also have antianaphylactic properties, but the doses required are greater than those necessary to inhibit histamine shock. All have local analgesic action and they may diminish capillary permeability to substances other than histamine. None of the antihistaminic agents, however, can take the place of vasoconstrictors, such as epinephrine and ephedrine, applied locally.

Uses.—The antihistamine compounds have the greatest therapeutic effect on nasal allergies, on seasonal hay fever more than on perennial vasomotor rhinitis. Relief is most probable from mild hay fever and predominantly sneezing symptoms, in the first part of the season, in a mild season, in favorable weather and in localities of low pollen or mold spore counts. Severe symptoms, advancing season, a heavy season and high pollen or spore counts diminish results. The drugs are of little use in the relief of nasal blocking, particularly common at the end of the season, and postseasonally. They do not prevent or effectively relieve the asthma that frequently complicates hay fever. Their effect is entirely palliative. Hay fever usually is treated most effectively by desensitization supplemented by the use of antihistaminic drugs when needed.

The antihistaminic drugs are useful in prevention and treatment of systemic allergic reaction to injections of allergenic substances, but such remedies as epinephrine, ephedrine and aminophylline are more active and, therefore, more urgently indicated. In relief of the dyspnea of asthma, particularly the acute paroxysm, the histamine antagonists are ineffective except as supplements to these other remedies. Spasmodic bronchial cough without dyspnea, most frequently encountered as a manifestation of allergy in children, often responds to antihistaminic drugs.

Urticaria, angioneurotic edema, serum sickness and reactions from penicillin, streptomycin, sulfonamides and other drugs usually are helped by the antihistaminic drugs. The pruritus is benefited most, edema less and serum sickness least. Other itching skin conditions among those frequently benefited by these drugs administered internally are atopic dermatitis (flexural eczema), contact dermatitis, pruritus ani and vulvae, generalized pruritus and insect bites, however, local application may give rise to serious sensitivity reactions. Dosage required for relief increases with the severity of symptoms.

Administration.—Antihistaminic drugs usually are given orally. The range of adult doses is 2 to 100 mg, depending on tolerance, response and the individual drug. The dose should be the smallest adequate to relieve symptoms. Optimum effect usually occurs 1 hour after ingestion, the effect lasting from 3 to 6 hours with

or mustard. Some drugs in this group also may be administered subcutaneously and in conjunction with allergenic extracts used for desensitization or other injectable remedies to which sensitivity has developed or its anticipated.

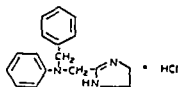
Toxicity.—All the antihistaminic drugs produce undesirable side reactions. The incidence and severity of these toxic actions and the dose required to produce them vary with each drug. People differ in sensitivity to the toxic actions of the group as a whole, and also in their response to particular drugs. Thus, certain persons may tolerate better a drug that has a high index of toxicity than one that has a lower index.

The most common untoward action is sedation. This varies from mild sedation to deep sleep, depending on the particular drug, the individual response and the dose. Inability to concentrate, dizziness and disturbed co-ordination are related to sedative action. After the antihistaminic drug has been used for 2 or 3 days, sedation frequently disappears. If the problem is not solved in this way, nor by the substitution of another antihistaminic compound, conjoint use of a cerebral stimulant such as methamphetamine or amphetamine may be advisable.

In some persons these drugs may produce such symptoms of excitation as insomnia, tremors, nervousness, palpitation and even convulsions. The side actions next in frequency are lassitude and muscular weakness, and then gastro-intestinal disturbances. The latter include various gastric discomforts, intestinal pain and diarrhea. Anorexia occurs often, as a result of both central nervous system disturbance and gastric irritation. Dryness of the mouth, throat and nose are common; although blood dyscrasias are rare, they too have been reported. Local application of dermatologic preparations for the relief of itching associated with either allergic or nonallergic dermatoses is of limited value and frequently is outweighed by local sensitivity reactions to the antihistamines.

Since prolonged use of these drugs eventually may produce other toxic visceral effects, patients under continuous treatment should be examined periodically. There also is evidence that continued use of antihistaminic drugs leads to decreased effectiveness (tolerance).

ANTAZOLINE HYDROCHLORIDE-U.S.P.—Antistine Hydrochloride (Ciba)—2-(N-Benzylanilinomethyl)-2-imidazoline hydrochloride—"Antazoline Hydrochloride, dried at 105° for 3 hours, contains not less than 98 per cent of $C_{17}H_{19}N_3 \cdot HCl$." U.S.P. The structural formula of antazoline hydrochloride may be represented as follows:



Physical Properties.—Antazoline hydrochloride forms white, odor-

less crystals with a bitter taste. It melts with decomposition between 232 and 238°. It is sparingly soluble in alcohol and water and practically insoluble in benzene and ether. A 1 per cent solution has a pH between 5.6 and 6.6.

Actions and Uses.—See the general statement on histamine-antagonizing agents. The therapeutic action of antazoline hydrochloride is weaker than that of most of the other antihistaminic drugs. It has particular virtues, however, in that it is milder and less irritating to tissues than other drugs of this group. Approximately 20 per cent of patients exhibit some side reactions, the most common of which are nausea and drowsiness.

phloc **some**
loc **stained**
wi **active**
constriction of the blood vessels is lacking, such immediate relief as may be occasionally observed probably is the result of slight local anesthetic activity.

Dosage.—Orally, as tablets, 100 mg. is given four times daily. If adequate response is obtained, the dosage may be reduced to 100 mg. twice daily.

For nasal application, an 0.5 per cent solution in isotonic sodium chloride may be instilled in the nose, or administered intranasally by a suitable nebulizer every 3 to 4 hours. The frequency of administration should be governed by response.

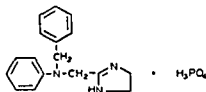
CIBA PHARMACEUTICAL PRODUCTS, INC.

Nasal Solution Antistine Hydrochloride 0.5%: 15 cc. dropper bottles. A solution containing 5 mg. of antazoline hydrochloride in each cubic centimeter.

Tablets Antistine Hydrochloride: 0.1 Gm.

U. S. patent 2,449,241. U. S. trademark 432,457.

ANTAZOLINE PHOSPHATE.—Antistine Phosphate (CIBA)—2-(N-Benzylanilinomethyl)-2-imidazoline phosphate—The structural formula of antazoline phosphate may be represented as follows:



Physical Properties.—Antazoline phosphate is a white, odorless, crystalline powder with a bitter taste. It melts with decomposition between 194 and 198°. It is soluble in water, sparingly soluble in methanol and practically insoluble in benzene and ether. The pH of a 2 per cent solution is about 4.5.

Actions and Uses.—See the general statement on histamine-antagonizing agents and the monograph on antazoline hydro-

chloride The phosphate is preferable to the hydrochloride for ophthalmic application in the management of ocular allergies because it produces less smarting and stinging Systemic therapy by oral administration of antazoline hydrochloride sometimes is desirable to supplement local treatment in the eye.

Dosage.—A 0.5 per cent isotonic solution of antazoline phosphate is employed for instillation in the eye. One or 2 drops are instilled in each eye every 3 or 4 hours or less frequently as required to relieve symptoms.

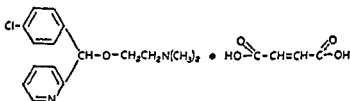
CIBA PHARMACEUTICAL PRODUCTS, INC.

Ophthalmic Solution Antistine Phosphate 0.5%: 15 cc. dropper bottles A solution containing 5 mg. of antazoline phosphate in each cubic centimeter. Preserved with 0.0065 per cent methylparaben and 0.0035 per cent propylparaben.

U. S. patent 2,449,241 U. S. trademark 432,437.

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REFERENCES



Physical Properties.—Carbinoxamine maleate is a white, odorless, bitter, crystalline powder with a melting point between 116 and 119°. It is very soluble in water, freely soluble in alcohol and in chloroform, and very slightly soluble in ether. The pH of a 1 per cent solution is between 4.6 and 5.1.

Actions and Uses.—See the general statement on histamine-antagonizing agents. Carbinoxamine maleate has as potent an antihistamine action and as low an incidence of side effects as has any other previously employed histamine antagonist. At its antihistamine level of action the drug exhibits comparatively weak atropine-like anticholinergic activity or ganglionic blockade in experimental animals, and it is not likely to produce cardiovascular or respiratory manifestations of such effects in human beings. It does not potentiate epinephrine or exhibit local anesthetic action.

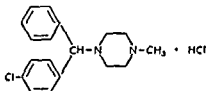
Dosage.—Carbinoxamine maleate is administered orally. The usual effective dosage for adults is 4 mg, three to four times daily. Larger doses of 6 to 8 mg usually are tolerated if needed to produce the desired antihistaminic effect. Children over 6 years of age usually respond to oral doses of 2 mg, three or four times daily; smaller doses may be required for younger children.

MCNEIL LABORATORIES, INC.

Elixir Clistin Maleate: 473 cc. and 3.78 liter bottles. An elixir containing 0.8 mg of carbinoxamine maleate in each cubic centimeter. Preserved with 0.1 per cent sodium benzoate and 0.02 per cent propylparaben.

Tablets Clistin Maleate: 4 mg

CHLORCYCLIZINE HYDROCHLORIDE-U.S.P.—Di-Paralene Hydrochloride (ABBOTT)—1-(*p*-Chlorobenzhydryl)-4-methylpiperazine hydrochloride.—“Chlorcyclizine Hydrochloride, dried at 105° for 3 hours, contains not less than 98 per cent of $C_{18}H_{21}ClN_2 \cdot HCl$ ” U.S.P. The structural formula of chlorcyclizine hydrochloride may be represented as follows.



Physical Properties.—Chlorcyclizine hydrochloride is a white, odorless, crystalline solid with a bitter taste. It melts between 222 and 227°. One part of chlorcyclizine hydrochloride is soluble in 1.6 parts of water, in 10.4 parts of alcohol and in 3.6 parts of chloroform, and is practically insoluble in benzene and ether. The pH of a 1 per cent solution is between 5.0 and 5.5.

Actions and Uses.—See the general statement on histamine-antagonizing agents. Chlorcyclizine hydrochloride has prolonged action and low incidence of toxic effects.

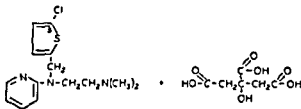
Dosage.—A dose of 50 mg. is given orally two or three times daily.

ABBOTT LABORATORIES

Tablets Di-Paralene Hydrochloride: 25 and 50 mg

U S patent 2,630,435 U S trademark 549,185.

mula of chlorothene citrate may be represented as follows:



Physical Properties.—Chlorothén citrate is a white, practically odorless solid. It melts between 116 and 118°. It is very slightly soluble in ether. The amounts that dissolve in the following solvents to form 100 cc. of solution are 2.5 Gm. in alcohol and 4.7 Gm. in water. When sodium hydroxide T.S. is added to a 1 per cent solution, the free base is obtained as an oil. The 1 per cent solution is clear and colorless, and has a pH between 3.9 and 4.1.

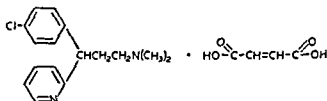
Actions and Uses.—See the general statement on histamine-antagonizing agents.

Dosage.—The average adult dose is 25 mg. administered orally.

WHITTIER LABORATORIES

Tablets Chlorothén Citrate: 25 mg.

CHLORPHENIRAMINE MALEATE—U.S.P.—Chlor-Trimeton Maleate (SCHERING).—2-[*p*-Chloro- α -(2-dimethylaminoethyl)benzyl]pyridine maleate—Chlorprophenpyridamine Maleate.—“Chlorpheniramine Maleate, dried at 105° for 3 hours, contains not less than 98 per cent of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$.” U.S.P. The structural formula of chlorpheniramine maleate may be represented as follows.



Physical Properties.—Chlorpheniramine maleate is a white, crystalline solid that melts between 130 and 135°. One part of chlorpheniramine maleate is soluble in 3.4 parts of water, in 10 parts of alcohol and in 10 parts of chloroform and is slightly soluble in benzene and ether. The pH of a 1 per cent solution is about 4.8.

Actions and Uses.—See the general statement on histamine-antagonizing agents. Chlorpheniramine maleate has good therapeutic efficacy and low incidence of side effects. It is comparable in therapeutic efficacy to other antihistaminics although administered in very low dosage. The effect of the drug may be prolonged by administering a special repeat action tablet form containing twice the average single dose, one-half of which is contained in an enteric-coated core to delay absorption.

Dosage.—The average oral dose for adults is 2 to 4 mg. A special repeat action tablet containing a total of 8 mg., half of which is enclosed by an enteric-coated core to prolong the action of the drug, may be administered to adults at intervals of 8 to 10 hours during the day and once at bedtime.

SCHERING CORPORATION

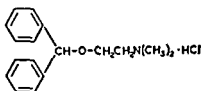
Syrup Chlor-Trimeton Maleate: 473 cc. and 3.78 liter bottles. A

flavored solution containing 0.5 mg. of chlorpheniramine maleate in each cubic centimeter.

Tablets Chlor-Trimeton Maleate: 4 mg.

Repetabs (*Repeat Action Tablets*) Chlor-Trimeton Maleate: 8 mg
U. S. patent 2,567,245 U. S. trademark 540,718.

DIPHENHYDRAMINE HYDROCHLORIDE-U.S.P.—Benadryl Hydrochloride (PARKE, DAVIS).—2-(Benzohydroxy)-N,N-dimethylethylamine hydrochloride — "Diphenhydramine Hydrochloride, dried at 105° for 3 hours, contains not less than 98 per cent of $C_{17}H_{21}NO \cdot HCl$." U.S.P. The structural formula of diphenhydramine hydrochloride may be represented as follows:



soluble in benzene and ether.

Actions and Uses.—See the general statement on histamine-antagonizing agents. In addition to its antihistaminic activity, this compound has moderate antispasmodic action, but the usefulness of this effect is limited to the relief of bronchial spasm. It produces a high incidence of sedation when used in full therapeutic doses.

Dosage.—The average adult dose is 50 mg orally, three or four times daily. Parenteral therapy should be used only to alleviate severe symptoms. An initial test dose of 10 mg should be administered parenterally. If sedation is not severe, subsequent doses may be increased to 20 to 50 mg every 2 or 3 hours.

PARKE, DAVIS & COMPANY

Capsules Benadryl Hydrochloride: 25 mg.

Elixir Benadryl Hydrochloride: 473 cc bottles. An elixir containing 2.5 mg of diphenhydramine hydrochloride in each cubic centimeter.

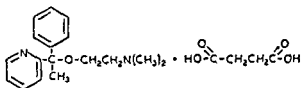
Kaptsals Benadryl Hydrochloride: 50 mg.

Powder Benadryl Hydrochloride: 14.17 Gm vials.

Solution Benadryl Hydrochloride: 10 cc. Steri-Vials. A solution containing 10 mg. of diphenhydramine hydrochloride in each cubic centimeter.

U. S. patent 2,421,714. U. S. trademark 416,252.

DOXYLAMINE SUCCINATE-U.S.P.—Decapryn Succinate (MERRELL).—2-[α -(2-Dimethylaminoethoxy)- α -methylbenzyl]pyridine succinate.—“Doxylamine Succinate, dried in a vacuum desiccator over phosphorus pentoxide for 5 hours, contains not less than 98 per cent of $C_{17}H_{22}N_2O \cdot C_4H_6O_4$ ” U.S.P. The structural formula of doxylamine succinate may be represented as follows:



Physical Properties.—Doxylamine succinate is a cream to white powder with a characteristic odor. It melts between 100 and 104°. It is very soluble in water, freely soluble in alcohol and chloroform and slightly soluble in benzene. The free base is obtained as an oil upon the addition of sodium hydroxide T.S. to a 5 per cent solution of doxylamine succinate. A 1 per cent solution of doxylamine succinate has a pH between 4.9 and 5.1.

Actions and Uses.—See the general statement on histamine-antagonizing agents. Doxylamine succinate produces a high incidence of sedation when used in full therapeutic doses.

Dosage.—The initial dose should be 12.5 mg. orally; this may be increased until the desired response is obtained or side effects become pronounced. The average adult dose is 12.5 to 25 mg.

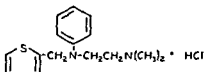
THE WM S MERRELL COMPANY

Syrup Decapryn Succinate: 473 cc bottles. A syrup containing 1.25 mg. of doxylamine succinate in each cubic centimeter.

Tablets Decapryn Succinate: 12.5 and 25 mg.

U. S. trademark 410,624.

METHAPHENILENE HYDROCHLORIDE-N.F.—*Diatrine Hydrochloride* (WARNER-CHILCOTT).—N,N-Dimethyl-N'-(α -phenyl)-N'-phenylethylenediamine hydrochloride.—“Methaphenilene Hydrochloride, dried at 105° for 4 hours, yields not less than 97.5 per cent and not more than 102.5 per cent of $C_{15}H_{20}N_2S \cdot HCl$ ” N.F. The structural formula for methaphenilene hydrochloride may be represented as follows.



Physical Properties.—Methaphenilene hydrochloride is a white to pale yellow, crystalline powder with a faint odor. It melts between 184 and 189°. It is soluble in water, sparingly soluble in alcohol and chloroform and practically insoluble in ether. The free base

is obtained as an oil upon adding sodium hydroxide T S to an aqueous solution of methaphenilene hydrochloride. A 2 per cent solution of methaphenilene hydrochloride has a pH between 4.8 and 5.6.

Actions and Uses.—See the general statement on histamine-antagonizing agents. Methaphenilene hydrochloride is therapeutically effective and induces low incidence of side reactions. It has a moderate tendency to cause gastro-intestinal irritation.

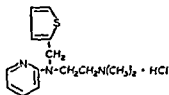
Dosage—The average adult dose is 50 mg. As with other anti-histaminic drugs, the dose used should be the smallest that will relieve symptoms.

WARNER-CHILCOTT LABORATORIES, DIVISION OF WARNER-HUDNUT, INC.

Tablets Diatrine Hydrochloride: 50 mg

U. S. patent, 2,526,943 U. S. trademark 506,769

as follows.



Physical Properties.—Methapyrilene hydrochloride is a white, crystalline powder with a faint odor. It melts between 159 and 162°. It is very soluble in water, freely soluble in alcohol and chloroform and practically insoluble in benzene and ether. The free base is obtained as an oil on the addition of 5 per cent sodium hydroxide to aqueous solutions of methapyrilene hydrochloride. A 5 per cent solution of methapyrilene hydrochloride has a pH between 5.9 and 6.4.

Actions and Uses.—See the general statement on histamine-antagonizing agents. The incidence of sedation is low with methapyrilene hydrochloride.

Dosage.—The average adult dose is 50 to 100 mg orally.

ABBOTT LABORATORIES

Tablets Thenylene Hydrochloride: 25 and 50 mg.

U. S. patent 2,581,868 U. S. trademark 434,475.

BLUE LINE CHEMICAL COMPANY

Elixir Methapyrilene Hydrochloride: 473 cc. and 3.78 liter bottles.

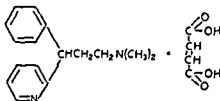
An elixir containing 6.76 mg. of methapyrilene hydrochloride in each cubic centimeter.

Tablets Methapyrilene Hydrochloride: 50 mg.

THE S. E. MASSENGILL COMPANY

Tablets Semikon Hydrochloride: 50 and 100 mg.

6 hours, contains not less than 99.0 per cent of $C_{20}H_{24}N_2O_4$." *N.F.* The structural formula of pheniramine maleate may be represented as follows:



Physical Properties.—Pheniramine maleate is a white solid with a faint aminelike odor. It melts between 104 and 108°. It is very soluble in alcohol and water, but only slightly soluble in benzene and ether. A 1 per cent solution has a pH between 4.3 and 4.9.

Actions and Uses.—See the general statement on histamine-antagonizing agents.

Dosage.—Pheniramine maleate is administered orally in dosage expressed in terms of the base. 1 mg. of pheniramine is equivalent, on the basis of molecular weight, to approximately 1.5 mg. of pheniramine maleate.

The usual adult dose is 25 mg., three times daily; children, according to age, may be given from 5 to 15 mg. three or four times daily.

SCHERING CORPORATION

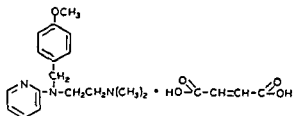
Elixir Trimeton Maleate: 473 cc. bottles. An elixir containing 1.88 mg. of pheniramine maleate in each cubic centimeter.

Tablets Trimeton Maleate: 37.5 mg. (equivalent to 25 mg. of pheniramine).

U. S. patent 2,567,245. U. S. trademark 509,760.

PYRILAMINE MALEATE—U.S.P.—Neo-Antergan Maleate (SHARP & DOHME).—Paraminy (COLUMBUS).—Star Maleate (BOWMAN).—methylaminoethyl)

"Pyrilamine Maleate, dried in a vacuum desiccator over phosphorus pentoxide for 5 hours, contains not less than 98 per cent of $C_{17}H_{23}N_3O_4 \cdot C_4H_4O_4$." *U.S.P.* The structural formula of pyrilamine maleate may be represented as follows.



Physical Properties.—Pyrilamine maleate is a white, crystalline powder with a faint odor. It melts between 100 and 102°. It is

amine maleate is clear and colorless, or nearly so, and has a pH between 4.5 and 5.5.

Actions and Uses.—See the general statement on histamine-antagonizing agents. The incidence of sedation is low with pyrilamine maleate.

Dosage.—The average adult dose is 25 to 50 mg. three to four times daily.

THE BOWMAN BROS. DRUG COMPANY

Tablets Statomin Maleate: 25 mg.

BUFFINGTON'S INC.

Tablets Paraminyl Maleate: 50 mg.

THE COLUMBUS PHARMACAL COMPANY

Tablets Pyramal Maleate: 50 mg.

PAUL B. ELDER COMPANY

Tablets Pyrilamine Maleate: 25 mg.

THE EVRON COMPANY, INC.

Tablets Pyrilamine Maleate: 25 mg.

KEITH-VICTOR PHARMACAL COMPANY

Tablets Pyrilamine Maleate: 25 and 50 mg.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Stengen Maleate: 25 and 50 mg.

RAYMER PHARMACAL COMPANY

Syrup Pyrilamine Maleate: 473 cc. and 3 78 liter bottles. A syrup containing 2.5 mg. of pyrilamine maleate in each cubic centimeter.

Tablets Pyrilamine Maleate: 25 and 50 mg.

WILLIAM H. RORER, INC.

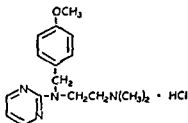
Tablets Thylogen Maleate: 25 and 50 mg.

SHARP & DCHME, DIVISION OF MERCK & CO, INC.

Tablets Neo-Antergan Maleate. 25 and 50 mg.

U. S. trademark 430,930

THONZYLAMINE HYDROCHLORIDE-U.S.P.—Neohetramine Hydrochloride (NEPERA) —2-[(2-Dimethylaminoethyl)(*p*-methoxybenzyl)amino]pyrimidine hydrochloride—"Thonzylamine Hydrochloride, dried at 105° for 2 hours, contains not less than 98 per cent of $C_{16}H_{22}N_4O \cdot HCl$ " U.S.P. The structural formula of thonzylamine hydrochloride may be represented as follows:



Physical Properties.—Thonzylamine hydrochloride is a white, crystalline powder with a faint odor. It melts between 173 and 176°. It is very soluble in water, freely soluble in alcohol and chloroform and practically insoluble in ether. The free base is obtained as an oil upon the addition of 5 per cent sodium hydroxide to aqueous solutions of thonzylamine hydrochloride. A 2 per cent solution of thonzylamine hydrochloride has a pH between 5.1 and 5.7.

Actions and Uses.—See the general statement on histamine-antagonizing agents. Although larger doses are required than for most other antihistamines, the degree of sedation is less severe.

severe

Dosage.—The average adult dose is 50 to 100 mg.

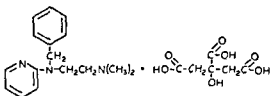
NEPERA CHEMICAL COMPANY, INC.

Syrup Neohetramine Hydrochloride: 475 cc bottles: A syrup containing 6.25 mg. of thonzylamine hydrochloride in each cubic centimeter.

Tablets Neohetramine Hydrochloride: 25, 50 and 100 mg

U. S. patent 2,465,865 U. S. trademark 501,673

TRIPLENNAMINE CITRATE.—Pyribenzamine Citrate (CIBA) —2-[Benzyl(2-dimethylaminoethyl)amino]pyridine citrate —N,N-Dimethyl-N'-benzyl-N'-(α -pyridyl)ethylenediamine citrate —The structural formula of tripeleennamine citrate may be represented as follows:



Physical Properties—Tripeleonnamine citrate is a white, crystalline powder with a bitter taste. It melts between 106 and 110°. It is very soluble in water, freely soluble in alcohol, very slightly soluble in ether and practically insoluble in benzene and chloroform. A 1 per cent solution has a pH of about 4.25.

Actions and Uses—Tripeleonnamine citrate is more palatable than the hydrochloride for oral administration of the drug in liquid form, otherwise it has no advantage over the hydrochloride and provides the same antihistaminic action. See the monograph on tripeleonnamine hydrochloride and the general statement on histamine-antagonizing agents.

Dosage—Tripeleonnamine citrate is administered in doses one-third greater than the hydrochloride because of the difference in the molecular weights of these compounds, 30 mg of tripeleonnamine citrate is equivalent to 20 mg of tripeleonnamine hydrochloride.

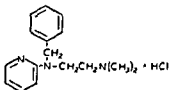
The average adult dose is 75 mg, four times daily. Infants and children usually tolerate doses of 15 to 60 mg, given at the same intervals.

CIBA PHARMACEUTICAL PRODUCTS, INC.

Elixir Pyribenzamine Citrate—473 cc and 378 liter bottles. An elixir containing 75 mg of tripeleonnamine citrate in each cubic centimeter.

U. S. patent 2,406,594 U. S. trademark 425,662

TRIPLEONNAMINE HYDROCHLORIDE—U. S. P.—Pyribenzamine Hydrochloride (CIBA)—N-Benzyl-N',N'-dimethyl-1-N-2-pyridylethylenediamine hydrochloride—"Tripeleonnamine Hydrochloride, dried at 105° for 3 hours, contains not less than 98 per cent of C₁₆H₂₁N₃·HCl" U. S. P. The structural formula of tripeleonnamine hydrochloride may be represented as follows.



Physical Properties—Tripeleonnamine hydrochloride is a white, crystalline powder which darkens slowly on exposure to light. Its solutions are practically neutral to litmus paper. One gram dis-

solves in 1 cc of water, 6 cc. of alcohol, 6 cc. of chloroform and about 350 cc. of acetone. It is insoluble in benzene, ether and ethyl acetate. It melts between 188 and 192°.

Actions and Uses.—See the general statement on histamine-antagonizing agents. The incidence of side reactions is low; gastrointestinal irritation is common but not severe, sedation is moderate and nervous system stimulation occurs occasionally. The drug may be injected parenterally (subcutaneously, intramuscularly or intravenously) whenever oral medication is not feasible or to produce a more prompt response in allergic emergencies, when used as a supplement to potent remedies such as epinephrine and aminophylline. A solution for injection also may be mixed extemporaneously for subcutaneous injection with allergens or other compatible remedies to minimize anticipated sensitivity reactions.

Dosage—The average adult oral dose is 50 mg., but, when indicated, larger doses of 100 to 150 mg. are tolerated by most people. For parenteral injection, a solution containing 25 mg. per cubic centimeter is administered in doses of from 12.5 to 25 mg. (0.5 to 1 cc.), two to four times daily. Depending on the parenteral route (subcutaneous, intramuscular, intravenous), the effect of such doses usually is obtained within 1 to 15 minutes and may persist for as long as 12 hours. Intravenous injection should be administered slowly with the patient recumbent. Intravenous drip using 25 mg. (1 cc.) diluted with 200 cc. of isotonic sodium chloride solution can be administered over a period of from 1.5 to 2 hours.

CIBA PHARMACEUTICAL PRODUCTS, INC.

Solution Pyribenzamine Hydrochloride: 1 cc. ampuls. A solution containing 25 mg. of tripeleannamine hydrochloride in each cubic centimeter.

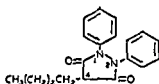
Tablets Pyribenzamine Hydrochloride: 25 and 50 mg.
U. S. patent 2,406,594

2

Analgesics

antipyretics, and sometimes are described as antipyretic analgesics; among these are salicylates, cinchophen derivatives, *p*-aminophenol derivatives (acetanilid and acetophenetidin) and pyrazolon derivatives (antipyrine and aminopyrine). These milder analgesics are not addicting and some, such as acetylsalicylic acid and acetophenetidin, are considered safe for sale without a prescription. With the advent of more effective drugs for the treatment of specific infections, the use of antipyretics as such has become less important. They may be detrimental if used against a fever without knowledge of its cause.

PHENYLBUTAZONE.—Butazolidin (GEIGY).—1,2-Diphenyl-4-butyl-3,5-pyrazolidinedione.—The structural formula of phenylbutazone may be represented as follows.



Physical Properties.—Phenylbutazone is a white or very light yellow powder with a slightly bitter taste and a very slight aromatic odor, with a melting point between 103 and 106°. It is freely

exerts an anti-inflammatory effect in delaying and minimizing local tissue reaction produced by chemical and physical irritants. Although its analgesic effect is less than that of acetylsalicylic acid in nonrheumatic conditions, phenylbutazone has been found to be clinically useful in the management of certain painful musculoskeletal disorders. Its mode of action in such conditions cannot be ascribed to a similarity with hormone drugs.

When administered orally, phenylbutazone is absorbed rapidly and completely; a single dose produces a peak plasma concentration in about 2 hours. When it is given intramuscularly as the sodium salt, the peak plasma level usually is not attained for 6 to 10 hours. The delay might be the result of precipitation of the drug, which is insoluble at the normal pH of the tissues. Stable plasma levels from 65 to 140 mg. per liter usually are reached on the third or fourth day following daily doses of 0.6 to 0.8 Gm. After a single dose, approximately one-third is concentrated in the plasma and is bound, almost entirely, to plasma protein. Increased dosage (over 0.8 Gm daily) is accompanied by a sharp increase in excretion of urinary metabolites, but with very little increase in the plasma concentration of the drug. This suggests that the protein-bound portion in the plasma acts as a drug depot and that, once the plasma proteins become saturated, the unbound excess is metabolized rapidly. At an oral dosage of 0.6 to 0.8 Gm. daily, the drug is metabolized at the rate of 15 to 25 per cent per day, so that a period of 7 to 10 days usually elapses before the drug disappears from the blood stream. Phenylbutazone is not excreted as such in any significant amount. At least three metabolites have been detected in the urine in
 duces a temporary decrease in
 tion of sodium and chlorine is
 compensatory diuresis and liberation of the excess retained sodium chloride. Potassium excretion is unaffected. Endogenous creatinine clearance studies indicate that glomerular filtration also is not affected by phenylbutazone, suggesting that decreased excretion of water and salt results from tubular reabsorption.

Phenylbutazone is useful chiefly in the treatment of gout and, to a lesser extent, psoriasis with arthritis, ankylosing spondylitis, rheumatoid arthritis and painful shoulder (peritendinitis, capsulitis, bursitis and acute arthritis of that joint). In gout, the use of the drug is associated with a reduction in serum uric acid. As with other agents, relapses are more prone to occur in rheumatoid conditions requiring continuous medication or alternative therapy. Phenylbutazone, because of the high incidence of untoward side effects, should not be used for the treatment of these conditions unless adequate trial of less hazardous therapeutic measures has proved unsuccessful. Its use in malum coxae senilis, osteoarthritis, osteoporosis and mixed arthritis is not recommended because in these conditions the incidence of toxicity outweighs the degree of clinical improvement.

Phenylbutazone has untoward side effects in approximately 40 per cent of patients, and it may be necessary to discontinue its use because of toxic effects in about 15 per cent. The most frequently incidence include water retention, pain, vertigo and stomatitis. vere reactions have been reported with bleeding, hepatitis, hypertension, transient psychosis, moderate leukopenia, agranulocytosis, thrombocytopenia and purpura without thrombocytopenia. Other less commonly observed side effects include central nervous

system stimulation, visual symptoms, anemia, lethargy, constipation, diarrhea, gastro-intestinal hemorrhage, fever and cardiac arrhythmia. Toxic side effects have been observed more frequently in women than in men.

Phenylbutazone is contraindicated in the presence of edema and in patients in whom there is danger of cardiac decompensation. Its use is inadvisable in patients with a history of peptic ulcer. Utmost caution is necessary when it is given to patients with a history of drug allergy or blood dyscrasia. In general, the use of phenylbutazone in conjunction with other potent drugs is not recommended because of the danger of increasing the incidence or severity of toxic reactions. The frequent occurrence of minor side effects and the occasional development of severe toxic manifestations require constant supervision of the patient by the physician. In addition to frequent clinical observations, weekly blood cell counts should be made during initial therapy and also at biweekly intervals when medication is continued over a prolonged period. Because sodium retention tends to occur, it is advisable to place patients on a restricted salt diet.

Dosage.—Phenylbutazone is administered orally. The recommended initial dosage is 0.3 to 0.8 Gm. daily, divided into three or four equal doses. Dosage in excess of 0.8 Gm. daily is inadvisable because this seldom produces greater therapeutic effect and may increase the toxic hazard. An average initial dosage of 0.6 Gm. daily, administered for 1 week, is considered adequate to determine the therapeutic effect of the drug. In the absence of a fever

conditions such as painful shoulder, medication should be discontinued a few days after relief of symptoms; in the event of relapse, therapy is resumed as needed to control symptoms. In the treatment of more chronic disorders, medication may be continuous at the minimal effective level required to maintain relief and freedom from acute exacerbations. Medication should be discontinued whenever toxic symptoms appear or whenever blood studies indicate any significant reduction in the formed elements. In some instances, therapy may be resumed at a lower dosage level when results of blood tests return to normal.

GEIGY PHARMACEUTICALS, DIVISION OF GEIGY COMPANY, INC.

Tablets Butazolidin: 0.1 Gm.

U. S. patent 2,562,830 U. S. trademark 559,912

SALICYLAMIDE.—Salamide (COLUMBUS).—The structural formula of salicylamide may be represented as follows:



Physical Properties.—Salicylamide is a white, almost odorless, crystalline solid, with a melting point between 139 and 142°. It is freely soluble in alkalis. The approximate amounts that dissolve at 25° in the following solvents to form 100 cc. of solution are 7 Gm. in alcohol, 1 Gm. in chloroform, 3 Gm. in ether, 5 Gm. in propylene glycol and 0.2 Gm. in water. Salicylamide is fairly stable to heat, moisture and light.

Actions and Uses.—Salicylamide, the amide of salicylic acid, shares the actions and uses of acetylsalicylic acid (aspirin). Clinical studies indicate that its analgesic potency is no greater, and may be somewhat less, than that of aspirin. Its antipyretic and anti-inflammatory or antiarthritic properties are not superior to those of aspirin. The over-all incidence of gastric intolerance to salicylamide is about the same as, or a little less than, that to aspirin; however, patients allergic to aspirin have been reported not to be sensitive to salicylamide. It can be used safely in place of salicylates whenever such medication is indicated.

Salicylamide is absorbed readily from the gastro-intestinal tract, but does not produce high salicylate levels in the serum. It is diffused widely throughout the tissues, excreted chiefly by the kidneys and, apparently, is not destroyed appreciably in the body. Since the toxicity of salicylamide compares closely with that of other salicylates, it should be employed with the same general precautions. The possibility of the development of sensitivity to salicylamide after its repeated use, particularly in patients already allergic to other salicylic acid compounds, should be kept in mind.

Dosage.—Salicylamide is administered orally, preferably after meals and with fluids to minimize gastric irritation. The dosage should not be less than that for aspirin. As a simple analgesic or antipyretic, single doses of 0.3 to 1 Gm. three times daily may be adequate, as an antirheumatic agent, doses of 2 to 4 Gm. three times daily (or 1 to 2 Gm. every 4 hours) may be prescribed, according to gastric tolerance, over periods of 3 to 6 days. For children, correspondingly smaller doses should be employed.

THE BOWMAN BROS. DRUG COMPANY

Hexett Tablets Salicylamide: 64 mg.

Tablets Salicylamide: 0.3 Gm.

CHEMIO PURO MANUFACTURING CORPORATION

Powder Salicylamide: Bulk; for manufacturing use.

THE COLUMBUS PHARMACAL COMPANY

Tablets Salamide: 0.325 Gm.

TRICHLOROETHYLENE-U.S.P.—Trilene (AYERST).—"Trichloroethylene contains not less than 99.5 per cent of C_2HCl_3 . It contains not less than 0.010 per cent and not more than 0.012 per cent of thymol as a preservative" U.S.P. The structural formula of trichloroethylene may be represented as follows:



Physical Properties.—Trichloroethylene is a clear, colorless or blue, mobile liquid. It has a characteristic odor resembling that of chloroform. It is slowly decomposed by light in the presence of moisture. It is not flammable. Trichloroethylene is practically insoluble in water. It is miscible with ether, alcohol and chloroform and dissolves most fixed and volatile oils.

Actions and Uses.—Trichloroethylene is a volatile liquid that produces prompt analgesia and anesthesia when inhaled. Its action resembles that of chloroform but is more rapid and less potent. It is suitable for inhalation as an analgesic agent only. Anesthetic concentrations do not produce complete muscular relaxation and are associated with tachypnea and bradycardia, sometimes accompanied by extrasystoles. These are signs of overdosage. Tachypnea is a sign that the first plane of anesthesia has been reached and should be regarded as a warning that administration has exceeded the analgesic level. With a suitable inhaler, self-administration under professional supervision is considered relatively safe for producing analgesia, usually without unconsciousness. Patients may experience slight dizziness and numbness the first few minutes. Irritation of respiratory passages (excessive salivation or secretion of mucus), nausea and vomiting are infrequent. If sufficient vapor is inhaled to produce unconsciousness, the mask automatically falls away from the face to prevent overdosage. Consciousness usually is restored within 20 to 30 seconds. Self-administration should not be permitted while the patient is alone.

Trichloroethylene as an analgesic mixture with air or oxygen is useful in obstetrics during labor and for delivery in conjunction with pudendal block or low spinal anesthesia. It also may be employed as an analgesic agent in minor surgical and dental procedures and in major operative procedures as an adjunct to light general anesthesia produced by other agents. When this drug is administered with inhalation anesthetics, standard anesthetic machines with a closed circuit may be used, provided they are adjusted so that trichloroethylene does not come into contact with soda lime. If contact with soda lime occurs in closed apparatus, persistent trigeminal neuralgia and other cranial palsies may result from the formation of toxic degradation products (acetylene dichloride, phosgene and carbon monoxide), formed by the interaction with soda lime.

Until further experience is gained, trichloroethylene is not recommended for use in patients with severe cardiac failure, active cardiac disease or toxemia of pregnancy. It never should be employed for induction anesthesia. Administration of epinephrine should be avoided whenever trichloroethylene is used.

Dosage.—Trichloroethylene is administered by inhalation by means of an inhaler device controlled by the patient or a mask or closed-circuit anesthetic machine controlled by an anesthetist. Premedication can be carried out according to the preference of

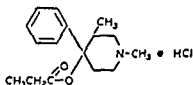
the physician. During labor or for minor surgical procedures, ten to twelve self-administered inhalations from a suitable device are taken by the patient at the onset of pain. When this agent is dropped on a mask or placed in a machine, a minimal concentration should be maintained at all times to avoid even the first plane of anesthesia. Trichloroethylene is nonexplosive; it is not flammable when mixed with air, but may become so when mixed with oxygen. When the latter mixture is used, there is risk of ignition especially when a cautery is employed. In such instances, admixture with air is preferable. Trichloroethylene is highly stable when stored in closed containers away from light. However, to avoid possible oxidation it is inadvisable to retain any unused portion in an anesthetic machine, such portions should be discarded. Trichloroethylene may be heated without decomposition; but, when its vapor, diluted with air, is exposed to a naked flame, decomposition occurs giving rise to hydrochloric acid and traces of phosgene. The agent or its vapor should not be allowed to come in contact with hot surfaces.

AYERST LABORATORIES, INC

Trilene: 6 cc. ampuls, 15 cc. tubes and 300 cc. bottles. Stabilized with 0.01 per cent thymol.

NONOPIATE, ADDICTING ANALGESICS

ALPHAPRODINE HYDROCHLORIDE.—Nisentil Hydrochloride (HOFFMANN-LA ROCHE).—1,3-Dimethyl-4-phenyl-4-piperidyl propionate hydrochloride.—The structural formula of alphaprodine hydrochloride may be represented as follows:



Physical Properties.—Alphaprodine hydrochloride is a white, crystalline, bitter powder with an aminelike odor and with a melting point between 218 and 221°. It is freely soluble in alcohol, in chloroform and in water and very slightly soluble in ether. Alphaprodine hydrochloride is stable to air, light and heat. The pH of a 1 per cent solution is between 4.5 and 5.2.

Actions and Uses.—Alphaprodine hydrochloride is a short-acting synthetic, narcotic analgesic agent chemically resembling meperidine but unrelated chemically to morphine. The analgesic action of alphaprodine, like that of morphine, is associated with euphoria, mild sedation, slight dizziness, itching and diaphoresis but is accompanied by less nausea, vomiting or respiratory depression. Its analgesic and depressant actions are somewhat less intense, but more prompt and of shorter duration, than those of morphine. The

relatively short duration of analgesic and sedative effect minimizes the hazard of respiratory depression resulting from the drug, but, if barbiturates are used concomitantly, the tendency to depressed respiration in the new-born may be increased because alphaprodine hydrochloride passes freely across the placental barrier. Its rapid onset and relatively short action permit considerable flexibility of administration. It is suited primarily for temporary analgesia in obstetrics, for urologic examinations and procedures (particularly cystoscopy), preoperatively in surgery and for minor surgical procedures, especially in orthopedics, ophthalmology, rhinology and laryngology. The drug may be used in conjunction with nerve block or inhalation anesthesia and with barbiturate sedation when allowance is made for the added depressant effect.

Alphaprodine hydrochloride produces little or no cumulative effect, but tolerance that involves the liability of addiction can develop. For this reason, the drug is subject to restriction as a narcotic. Although it is intended only for temporary analgesia, the potential addiction liability of its prolonged use for other purposes or by addicts as a substitute for other narcotic analgesics should be kept in mind.

Dosage.—Alphaprodine hydrochloride is administered in solution by subcutaneous injection; intravenous injection may be employed when very rapid and brief analgesia is desired. The average initial subcutaneous dose is 40 to 60 mg., depending on the patient's weight, similar doses may be repeated at 2-hour intervals. A dose of 40 mg. is suggested for a patient weighing 50 Kg. (110 lb.). Such a dose usually produces analgesia within 5 minutes and lasts for an average of 2 hours. In obstetrics, the initial dose may be given at any time after the cervix has begun to dilate. Depression of fetal respiration resulting from the drug is obviated

hydrochloride is an effective antidote

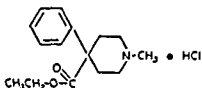
HOFFMANN-LA ROCHE, INC

Solution Nisentil Hydrochloride 4%: 1 cc. ampuls. A solution containing 40 mg. of alphaprodine hydrochloride in each cubic centimeter. Preserved with 0.45 per cent phenol.

Solution Nisentil Hydrochloride 6%: 1 cc. ampuls and 10 cc. vials. A solution containing 60 mg. of alphaprodine hydrochloride in each cubic centimeter. Preserved with 0.45 per cent phenol.

U. S. patent 2,498,433 U. S. trademark 519,750

MEPERIDINE HYDROCHLORIDE—U. S. P.—Demerol Hydrochloride (BROWN and WINTHROP-STEARN) —Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride—The structural formula may be represented as follows.



Physical Properties.—Meperidine hydrochloride occurs as a fine, white, odorless, crystalline powder. It is soluble in water and in alcohol and sparingly soluble in ether. Aqueous solutions are acid to litmus.

Actions and Uses.—Meperidine hydrochloride possesses a slight atropine effect and predominant codeinelike analgesic properties. It is capable of depressing the cardiac vagus of the anesthetized animal to the point where faradic stimulation fails to elicit any cardiac effect. Such responses are reversible.

The spasmolytic action of meperidine hydrochloride is due in

is slightly greater than that of codeine and persists for 2 to 4 hours. It may last 6 hours with large or repeated doses.

The drug possesses moderate addiction liability evidenced by withdrawal symptoms observed in susceptible individuals. The development of tolerance to the drug has been demonstrated in man, and it may be substituted for morphine to prevent the morphine withdrawal syndrome.

The development of psychic dependence on meperidine hydrochloride also is likely since the drug produces in some individuals a euphoria that lasts for an hour or more, depending on the dose.

Meperidine hydrochloride is indicated for the alleviation of pain, particularly pain of spastic origin, and for the majority of conditions in which morphine or other opium alkaloids are generally employed. In obstetrics it may be used to lessen the severity of labor pains and, in conjunction with barbiturates or scopolamine, to produce obstetric amnesia.

The drug may produce contraction of the upper gastro-intestinal tract intermediate in intensity between that produced by codeine and that by morphine. Typical attacks of biliary colic occasionally have followed its use in patients with biliary tract disease. When meperidine hydrochloride is given after cholecystectomy, patients show increased pressure in the common bile duct. Thus, in the gastro-intestinal tract, the spasmolytic effect of meperidine

lower intestine
conditions the average
0.1 Gm., administered
pain, from 50 mg. to

0.1 Gm. may be required.

For the production of analgesia in obstetrics, 0.1 Gm. is given intramuscularly as soon as contractions occur at regular intervals.

If labor is rapid or if the cervix is thin and dilated (2 to 3 cm. or more) the second dose may be given as soon as one-half hour after the first one. A third dose may be necessary an hour or two later, depending on progress.

Therapeutic doses produce a slight to moderate sedative action that shows wide individual variability, being especially prominent in the aged. Thus, barbiturates used with meperidine hydrochloride to produce amnesia are effective in considerably smaller doses than when used alone. One of the barbiturates may be given when the cervix is dilated 4 or 5 cm. or when the third dose of meperidine hydrochloride is administered. In the majority of cases this procedure will ensure adequate amnesia for 4 to 6 hours.

GEORGE A. BREON & COMPANY

Solution Demerol Hydrochloride: 2 cc. ampuls and 30 cc. vials. A solution containing 50 mg. of meperidine hydrochloride in each cubic centimeter.

Tablets Demerol Hydrochloride: 50 mg.

WINTHROP-STEARNs, INC.

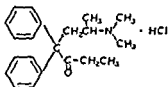
Powder Demerol Hydrochloride: 15 Gm. vials.

Solution Demerol Hydrochloride: 1 and 2 cc. ampuls and 30 cc vials. A solution containing 50 mg. of meperidine hydrochloride in each cubic centimeter.

Tablets Demerol Hydrochloride. 50 and 100 mg.

U. S. patent 2,167,351 U. S. trademark 381,130.

METHADONE HYDROCHLORIDE-U.S.P.—Adanon Hydrochloride (WINTHROP-STEARNs). — Methadon — *d,l*-6-Dimethylamino-4,4-diphenyl-3-heptanone hydrochloride. — "Methadone Hydrochloride, dried at 105° for 1 hour, contains not less than 98.5 per cent of $C_{21}H_{27}NO \cdot HCl$ " U.S.P. The structural formula of methadone hydrochloride may be represented as follows.



common alkaloidal reagents. The pH of a 1 per cent solution of methadone hydrochloride is between 4.5 and 6.5.

Actions and Uses.—The term methadone refers to a mixture of the *d* and *l* isomers. The actions of methadone hydrochloride are similar to those of morphine. The *l* isomer is five times as potent as the *d* isomer. Except when taken orally, it causes less nausea and emesis than morphine and, in minimal analgesic doses causes less respiratory depression. Methadone hydrochloride seems slightly less sedative than morphine, but its action lasts longer than that of morphine, and it is better absorbed when administered orally.

Methadone hydrochloride induces addiction and, after long administration, may cause withdrawal symptoms, but they appear more slowly and are less severe than those caused by similar administration of morphine. Methadone hydrochloride may be substituted for morphine to prevent or alleviate morphine withdrawal symptoms.

Methadone hydrochloride may be used as an analgesic for moderate and severe pain. It also is antitussive, but for this purpose codeine is preferred because it has less addiction liability.

Dosage.—Adults, 5 to 15 mg. depending on the intensity and etiology of the pain. The usual dose is 7.5 mg. orally every 3 to 4 hours.

When necessary, the drug may be administered parenterally either intramuscularly or subcutaneously, but because of its slight local irritant effects it should not be administered by either route in doses larger than 2.5 to 10 mg. It should not be given intravenously.

ABBOTT LABORATORIES

Solution Methadone Hydrochloride: 1 cc. ampuls and 20 cc. vials. An isotonic sodium chloride solution containing 10 mg. of methadone hydrochloride in each cubic centimeter. The 20 cc. vial is preserved with 0.9 per cent benzyl alcohol.

Syrup Methadone Hydrochloride: 473 cc. and 3.78 liter bottles. A syrup containing 0.34 mg. of methadone hydrochloride in each cubic centimeter.

S. E. MASSENGILL COMPANY

Solution Methadone Hydrochloride: 1 cc. ampuls and 10 cc. vials. A solution containing 10 mg. of methadone hydrochloride in each cubic centimeter. The vials are preserved with 0.5 per cent chlorobutanol.

Tablets Methadone Hydrochloride: 2.5, 5 and 7.5 mg.

THE UPJOHN COMPANY

Solution Methadone Hydrochloride: 30 cc. vials. A solution containing 10 mg. of methadone hydrochloride in each cubic centimeter.

Tablets Methadone Hydrochloride: 10 mg.; for hypodermic use.

WINTHROP-STEARNs, INC.

Elixir Adanon Hydrochloride: 473 cc. bottles An elixir containing 1 mg. of methadone hydrochloride in each cubic centimeter.

Solution Adanon Hydrochloride: 2 cc. ampuls and 20 cc. vials. A solution containing 5 mg. and 10 mg., respectively, of methadone hydrochloride in each cubic centimeter.

Syrup Adanon Hydrochloride: 473 cc. bottles A syrup containing 0.33 mg. of methadone hydrochloride in each cubic centimeter.

Tablets Adanon Hydrochloride: 2.5, 5, 7.5 and 10 mg.

U. S. trademark 435,101

OPIUM PRINCIPLES AND DERIVATIVES

Morphine is a complex derivative of phenanthrene. It contains two OH groups (one phenolic, the other alcoholic) in which the hydrogen can be replaced by either alkyl or acid radicals.

The more important alkyl ethers are the monomethyl (codeine), the dimethyl (thebaine) and ethyl-morphine. Heroin is the diacetyl ester derivative.

The nature of these radicals—acid or alcoholic, aromatic or aliphatic—modifies the actions quantitatively. Replacement of one hydroxyl by a methyl group (codeine) diminishes the narcotic and respiratory depressant actions but increases the convulsant action. When both OH groups are replaced by acids (diacetyl morphine), the narcotic effects are stronger than with codeine, and the convulsant action is weaker than with morphine. All opiate analgesics except codeine may be given by slow intravenous injection.

The central actions of all these morphine derivatives are qualitatively identical, but they present quantitative differences of some practical importance.

must be continued for some time and for patients who do not tolerate morphine.

Ethyl-Morphine is intermediate between morphine and codeine in all respects. The hydrochloride is the most frequently used form.

Diacetyl-Morphine (heroin) is similar to morphine. It was introduced originally with the claim that therapeutic doses lessen the cough reflex and slow the respiration, while the inspirations are deeper and more powerful. Independent workers, however, have shown that there is no real difference from morphine in these respects. Diacetyl-morphine is as effective as morphine in cough, but not more so, it is less effective against dyspnea; it is more liable to produce habit and toxic effects.

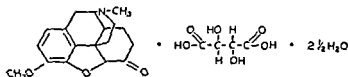
Nalorphine, although it exerts little or no analgesic effect, has

been included in this section because of its chemical relationship to morphine.

The major deficiencies of morphine as a therapeutic agent are that it causes nausea, vomiting, constipation and undesirable respiratory depression, and it is quite likely to produce tolerance and addiction.

A comparative analysis of the actions of morphine with other useful, potent analgesics is presented in the accompanying table. It should be recognized that such a tabulation is neither complete nor absolutely accurate for all dosage ranges and differing conditions of administration. For example, tolerance and physical dependence can be developed by any compound in this list if large doses are administered at frequent intervals.

FOR ANALGESIA	RELATIVE PO- TENCY (ME- PERI- DINE = 1)	ORAL EFFEC- TIVE- NESS	RESPIRATORY DEPRESSION	DEVELOP- MENT OF TOLERANCE: RATE	ADDIC- TION LIA- BILITY
	AVER- AGE EFFEC- TIVE DOSE, Mg	AVER- AGE DUR- ATION, HOURS	NAUSEA, VOMITING & CONSTI- PATION	EXTENT	
Levorphanol	50 2	Good 5-6	Marked Less marked	Less rapid Complete	Very great
Dihydromor- phinone	50 2	Fair 3	Marked Less marked	Rapid Complete	Very great
Metopon (Oral)	33 3	Good 3	Moderate Minimal	Less rapid Complete	Great
Heroin	20 5	Poor 2-3	Marked Less marked	Rapid Complete	Very great
Morphine	10 10	Poor 4-5	Marked Marked	Rapid Complete	Very great
Methadone	10 10	Good 4-5	Marked Less marked	Less rapid Less complete	Moderate
Meperidine	1 100	Fair 2-3	Moderate Moderate	Rapid Incomplete	Moderate
FOR ANTITUSSIVE ACTION					
Dihydroco- deinone	5	Good 4-5	Minimal Minimal	Slow	Low
Codeine	30	Good 2-3	Minimal Minimal	Slow	Very low



Physical Properties.—Dihydrocodeinone bitartrate is a white, odorless, crystalline powder. It is freely soluble in water and slightly soluble in alcohol. An 0.1 M solution in freshly boiled and cooled water has a pH between 3 and 4.

Actions and Uses.—Dihydrocodeinone bitartrate is essentially similar in action to codeine salts, but when compared with codeine on the basis of weight it is more active and more addicting. It is useful primarily as an antitussive, in the same manner as codeine, but has no clear-cut advantage.

Dosage.—Adults, 5 to 15 mg., three or four times in 24 hours. The higher dosage is rarely necessary. Children 2 years of age or older may be given one-half the adult dose, younger children one-quarter the adult dose.

ENDO PRODUCTS, INC.

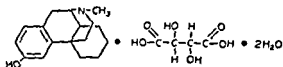
Powder Hycodan Bitartrate: 1 Gm., 5 Gm. and 10 Gm. bottles.

Syrup Hycodan Bitartrate: 475 cc and 3.74 liter bottles. A syrup containing 1 mg. of dihydrocodeinone bitartrate in each cubic centimeter.

Tablets Hycodan Bitartrate: 5 mg.

U. S. trademark 399,421

LEVORPHANOL TARTRATE.—Levo-Dromoran Tartrate (HOFFMANN-LA ROCHE).—Levo-3-hydroxy-N-methylmorphinan tartrate dihydrate.—The structural formula of levorphanol tartrate may be represented as follows:



Physical Properties.—Levorphanol tartrate is a white, odorless, bitter crystalline powder, with a melting point between 114 and 116°. It is very slightly soluble in chloroform and ether. The approximate amounts that dissolve at 25° in the following solvents to form 100 cc. of solution are: 0.9 Gm. in alcohol and 2 Gm. in water. Levorphanol tartrate is stable to light, air, heat and

moisture. The pH of the 0.2 per cent solution is between 3.4 and 4.0.

Actions and Uses.—Levorphanol tartrate, a potent, synthetic analgesic related chemically and pharmacologically to morphine, produces a similar intensity of analgesia in much smaller doses and seems to be somewhat longer acting. Available experimental evidence indicates that the toxicity of levorphanol roughly parallels its analgesic activity. With corresponding analgesic doses, its margin of safety is approximately equal to that of morphine.

Levorphanol tartrate is useful for the relief of severe pain and may be employed for the management of intractable pain caused by cancer and other tumors, severe trauma, biliary and renal colic, gangrene and myocardial infarction. It is also useful for preoperative medication and postoperative relief of pain.

Levorphanol tartrate produces side effects similar to those of morphine, except that it is less likely to cause constipation. Pruritus or sweating occurs infrequently. Nausea, emesis and dizziness occur more commonly in ambulatory patients, as occurs with the use of other narcotic analgesics. The contraindications are the same as for morphine. Because the drug exhibits an addiction liability similar to that of morphine, the same precautions should be observed as for other addicting analgesics.

Dosage.—Levorphanol tartrate is administered either orally or subcutaneously. The recommended average adult dose is 2 to 3 mg. Dosage may be subject to adjustment, in accordance with the age and weight of the patient, the severity of pain and the development of tolerance. As with other addicting analgesics, initial dosage should be as low as possible in the management of intractable pain to delay the development of tolerance.

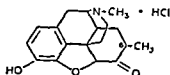
HOFFMANN-LA ROCHE, INC

Solution Levo-Dromoran Tartrate: 1 cc ampuls and 10 cc. vials. A solution containing 2 mg of levorphanol tartrate dihydrate in each cubic centimeter. Ampul solutions are preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben; vial solutions are preserved with 0.5 per cent phenol.

Tablets Levo-Dromoran Tartrate: 2 mg. Each tablet contains 2 mg. of levorphanol tartrate dihydrate.

U S patent 2,524,855 U S trademark 540,115.

METOPON HYDROCHLORIDE. — 6-Methyldihydromorphinone hydrochloride.—The structural formula of metopon hydrochloride may be represented as follows.



Physical Properties.—Metopon hydrochloride is a white, odorless,

of about 50.

Actions and Uses.—Metopon hydrochloride is a morphine derivative which is effective orally and appears to possess less undesirable side actions than the parent compound. Tolerance and dependence develop less rapidly and disappear more quickly than with morphine, but the drug must be employed with the usual care to avoid narcotic addiction.

Metopon hydrochloride is recommended only for the control of severe persistent pain. It should not be used as a preanesthetic medication because it may cause unpredictable and severe respiratory depression when used in conjunction with an inhalation anesthetic.

Dosage.—Three milligrams is approximately equivalent in analgesic effect to 10 mg. of morphine. This dose should be repeated only on the recurrence of pain; regular administration is to be avoided, since it tends to develop tolerance and addiction. When tolerance to morphine or other narcotics is present, cross tolerance to metopon may be expected and larger doses may be required. It is desirable to keep the dose at the lowest level that will provide pain relief.

PARKE, DAVIS & COMPANY

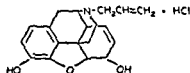
Capsules Metopon Hydrochloride: 3 mg.

SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Capsules Metopon Hydrochloride: 3 mg.

NALORPHINE HYDROCHLORIDE

as follows:



Physical Properties.—Nalorphine hydrochloride is a white, odorless, crystalline powder, with a melting point between 265 and 270°. It is completely soluble in water, very slightly soluble in chloroform and practically insoluble in ether. The amount that dissolves in alcohol to form 100 cc. of solution is 6.1 Gm. The pH of a 0.5 per cent solution is between 4.4 and 5.5.

Actions and Uses.—Nalorphine is a derivative of morphine and, therefore, is subject to control under the federal narcotic law. Its action, however, is considered to be pharmacologic rather than chemical, because it exerts little or no analgesic effect and antagonizes such narcotic analgesics as morphine, meperidine and metha-

done. Nalorphine promptly reverses the respiratory depression and increases both the minute volume and rate of respiration in patients narcotized by large doses of these compounds. It also prevents the occurrence of respiratory depression when administered 30 minutes prior to a large therapeutic dose of morphine. The drug also may reverse the fall in blood pressure. The decrease in pulse

the superficial and deep

3. It alters the electro-
ep sleep to that of the
orphine and its deriva-

tives. It is not active against the depression produced by barbiturates, cyclopropane or ethyl ether.

Nalorphine as the hydrochloride is useful as an antidote in the treatment of accidental overdosage and to combat alarming symptoms of extreme narcosis produced by morphine and its analgesic derivatives, as well as meperidine and methadone. It is not useful as a cure or for the relief of narcotic addiction. The drug may be administered 10 minutes prior to delivery of parturient women to overcome meperidine and other narcotic-induced respiratory depression of the newborn. Its use in excessively narcotized subjects should not exclude other appropriate supportive therapy. Until the effects of long-term use become known, or are found to be harmless, it should be used only for acute conditions.

Nalorphine hydrochloride appears to be relatively safe, although the lethal dose has not been established for man. Although doses up to 40 mg per kilogram of body weight are tolerated by experimental animals, it is considered advisable to limit single doses in man to not more than 40 mg. Side effects include—

by dysphoria

sweating

cold flashes

venous injection of morphine, sometimes is observed. In morphine addicts, administration of the drug may be followed by typical abstinence changes, such as yawning, rhinorrhea, lacrimation, goose flesh, vomiting and restlessness.

Dosage.—Nalorphine hydrochloride is administered as a solution by injection intravenously, intramuscularly or subcutaneously, depending on the rapidity of the action desired. Intravenously, the usual adult single dose is 5 to 10 mg, repeated in 10 to 15 minutes if adequate increase in pulmonary ventilation is not obtained. The effect of the drug lasts from 2 to 3 hours and the total dosage to be given depends on the degree and duration of the depression. In severe cases of poisoning, doses as high as 40 mg. may be employed.

SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Solution Nalline Hydrochloride. 1 and 2 cc ampuls. A solution containing 5 mg. of nalorphine hydrochloride in each cubic centimeter. Stabilized with 0.2 per cent sodium bisulfite and buffered with 1.5 per cent sodium citrate.

U. S. patent 2,364,833. U. S. trademark 569,220.

3

Anesthetics

GENERAL ANESTHETICS

General anesthetics progressively depress the central nervous system. Many of them, administered in moderate doses, induce analgesia before loss of consciousness occurs. The various reflex mechanisms likewise are inhibited in orderly progressions characteristic of each drug. This process is reversible by withdrawal of the agent.

Such drugs must enter the blood stream to be carried to the nervous system. Portals of entry are the lungs (inhalation); the gastro-intestinal tract (oral or rectal administration); direct intravenous injection. Certain agents may be given by any of the three routes (e.g., ether).

The effect of these drugs is estimated largely on the basis of changes in the various reflexes as the concentration increases in the central nervous system. General anesthesia thus is divided into stages and planes. Some drugs formerly looked upon as hypnotics now are used in much larger doses as general anesthetics (e.g.,

CYCLOPROPANE-U.S.P. — Trimethylene. — "Cyclopropane contains not less than 99 per cent by volume of C_3H_6 " U.S.P. The structural formula of cyclopropane may be represented as follows:



Physical Properties.—Cyclopropane is a colorless gas of characteristic odor, resembling that of petrolatum benzin, and having a pungent taste. One volume of cyclopropane dissolves in about 2.7 volumes of water at 15° . It is freely soluble in alcohol and soluble in fixed oils.

Actions and Uses.—Cyclopropane is the most powerful of the gaseous anesthetic agents; concentrations are from 15 per cent of cyclopropane and 85 per cent of oxygen up to the rarely and briefly used 40 per cent of cyclopropane and 60 per cent oxygen. It should be noted, however, that only 3.5 per cent (by volume) of ether is

required to induce the same plane of anesthesia that is induced with 20 per cent (by volume) of cyclopropane. Thus 96.5 per cent of oxygen may be used with ether, while only 80 per cent may be used with cyclopropane, for this particular depth of anesthesia. The high anesthetic potency of cyclopropane, as compared with other hydrocarbons, is advantageous because high concentrations of oxygen may be used. The rate of diffusion of cyclopropane is about twice that of ethylene. Cyclopropane is eliminated less rapidly than ethylene but much faster than ether. Induction and recovery with cyclopropane therefore are slower than with ethylene but more rapid than with ether.

Cyclopropane affects the autonomic tissue of the heart more than ether or chloroform. In high concentrations it heightens the irritability of this tissue and induces predisposition to cardiac arrhythmias. This effect is enhanced by the simultaneous use of epinephrine. For and the use of propane anesthesia; . . .
 thetic agents, do . . .

preoperative sedation with respiratory depressants must be used with caution. Since the signs of Guedel for other anesthetic agents do not apply to cyclopropane, familiarity with the signs of the stages of anesthesia for cyclopropane is absolutely essential in the administration of this agent.

Careful operating-room technic should be observed to avoid production of electrostatic sparks, open flames and cautery should be handled with the same precautions as those for other explosive or flammable anesthetics.

The advantages of cyclopropane consist in its effectiveness in concentrations that provide an adequate supply of oxygen and less excitement during induction. Its disadvantages include explosibility when oxygen-rich mixtures are employed, lack of respiratory stimulation, difficulty in detection of the planes of anesthesia by those unfamiliar with its administration, occasional laryngospasm and tendency to produce cardiac arrhythmias, postanesthetic headache and poor muscular relaxation.

Dosage.—Cyclopropane is furnished in compressed form in metal

per cent. The remainder of the mixture should consist of a minimum of 20 per cent oxygen, but oxygen should be supplied in quantities adequate for physiologic needs. When other anesthetics also are used in combination, less cyclopropane is required.

Caution.—Cyclopropane is flammable and its mixture with oxygen or air may explode when brought in contact with a flame or other causes of ignition.

OHIO CHEMICAL & SURGICAL EQUIPMENT CO.

Cyclopropane: 151.4, 378.5 and 870.6 liter cylinders.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Cyclopropane: 151 4, 378.5 and 757 liter cylinders

TRIBROMOETHANOL-U.S.P.—**Avertin** (WINTHROP-STEARNS).—**Tribromoethyl Alcohol**—"Tribromoethanol dried over sulfuric acid for 4 hours contains not less than 99 per cent of $C_2H_3Br_3O$ " *U.S.P.* The structural formula of tribromoethanol may be represented as follows.



Physical Properties.—Tribromoethanol occurs as a white, crystalline powder, with a slight aromatic odor and taste. It is unstable in air. Both aqueous and alcoholic solutions of tribromoethanol decompose on exposure to light. One gram of tribromoethanol dissolves in about 35 cc. of water at 25°. It is very soluble in amylene hydrate.

Actions and Uses.—Tribromoethanol is administered rectally as a solution in amylene hydrate for basal anesthesia. Dosage should not be sufficient to cause complete anesthesia. Basal narcosis with a solution of tribromoethanol diminishes the amount of inhalation anesthetic necessary to establish and maintain complete anesthesia. A prolonged period of sleep usually follows termination of inhalation anesthesia, during this afterperiod careful nursing care and continuous vigilance are necessary to maintain an open airway and to prevent the cyanosis and respiratory failure that sometimes follow. Ephedrine, caffeine with sodium benzoate and oxygen therapy are effective antidotes against respiratory and circulatory depression occurring from tribromoethanol.

Tribromoethanol is useful in the control of convulsive conditions such as tetanus. In tetanus it is used (for several days, if necessary) in repeated doses in conjunction with administration of tetanus antitoxin. It must be remembered, however, that there is danger of profound respiratory depression.

acidosis.

Dosage.—"For each kilogram of body weight, rectally, 60 to 80 mg, not to exceed 8 cc for women, 10 cc for men" *U.S.P.*

Solutions of tribromoethanol are administered rectally in 2.5 per cent solution in warm distilled water at a temperature not exceeding 40°. A small quantity of the solution should be tested just before administration with the congo red indicator supplied with the preparation. The color of the solution should match that of an equal amount of distilled water containing an equal quantity of the congo red indicator. If the colors do not match, the presence of

irritant hydrobromic acid and *di*-bromacetaldehyde is indicated, and the solution should be discarded.

The ordinary maximum dose for basal anesthesia is 80 mg. of tribromoethanol (40 mg. of amylene hydrate) per kilogram of body weight. The dose for young, vigorous persons sometimes may be increased to 90 or 100 mg. of tribromoethanol. A dose of 30 to 50 mg. per kilogram usually is sufficient for amnesia and is not accompanied by depression of the respiration or circulation. As the amylene hydrate adds materially to the narcotic effect, it should be remembered that, with each dose of tribromoethanol, half this dose by weight of amylene hydrate is administered.

The total amount administered should not exceed 6 to 8 Gm. of tribromoethanol for women, and 9 to 10 Gm. for men, regardless of weight. Dosage tables are supplied by the firm.

Solutions of tribromoethanol never should be employed by those inexperienced in its use except under expert supervision.

"Caution.—The total amount administered should not exceed 8 Gm. for women or 10 Gm. for men, regardless of body weight." U.S.P.

WINTROP STEARNS, INC.

Solution Avertin with Amylene Hydrate: 25 and 100 cc. bottles. A solution containing 1 Gm. of tribromoethanol and 0.5 Gm. of amylene hydrate in each cubic centimeter.

U. S. trademark 233,204

VINYL ETHER—U.S.P.—Vinethene (SHARP & DOHME).—Divinyl Oxide.—"Vinyl Ether for anesthesia consists of about 96 per cent of C_4H_6O and about 4 per cent of dehydrated alcohol. It may contain 0.025 per cent of a suitable preservative." U.S.P. The structural formula of vinyl ether may be represented as follows:



Physical Properties.—Vinyl ether occurs as a clear liquid having a characteristic odor. It is colorless or has a slight purple fluorescence derived from the preservative. It boils between 29 and 31°. It is slightly soluble in water but is miscible with alcohol, acetone, chloroform and ether.

Actions and Uses.—Vinyl ether is an inhalation anesthetic to be used for short anesthesia or induction. Its action is more rapid than that of ether, U.S.P. Since the safety zone of surgical anesthesia is narrow, only constant close observation of the patient will enable the anesthetist to avoid dangerous overdosage. Properly watched, this rapid induction and recovery are of advantage in short anesthetics. The patient is completely oriented and ambulant within a few minutes. To prevent recovery before the surgical procedure is completed, vinyl ether must be administered continuously.

The anesthetist should familiarize himself thoroughly with the properties of vinyl ether before employing it. The eye signs that

indicate stages of other anesthetics are entirely unreliable in vinyl ether anesthesia. The most important signs in determining the extent of the anesthesia are the rate, depth, regularity and smoothness of respiration. Although there is occasionally an increased secretion of mucus during maintenance even when atropine is administered, postoperative complications are infrequent. Nausea and vomiting occur in about 5 per cent of patients and muscular relaxation is often poor. Vinyl ether is irritating to the skin, especially when combined with pressure (as finger pressure or holding the mask too tight). A light film of petrolatum or other lubricant should be applied to the skin of the patient's face.

Under no circumstances should the anesthetic be pushed, and if proper relaxation and anesthesia are not obtained with low concentrations other agents should be employed. Overdosage is likely to cause anoxemia, cyanosis and respiratory failure. Under such circumstances the anesthetic must be discontinued, oxygen administered with artificial respiration, and measures taken to stimulate respiration and provide an adequate airway between the lungs and the atmosphere. The explosive and fire hazards of vinyl ether are equal to those of ether.

Vinyl ether is intended primarily for use in minor surgical operations of short duration, and in dentistry where gas anesthesia is not available. It is also useful as an induction anesthetic, particularly in children. It has been used extensively during postpartum obstetric procedures. Its rapid action with depression of fetal respiratory movements before producing analgesia in the mother practically precludes its use during labor.

As with most other anesthetic agents, age, cardiovascular disease, renal insufficiency or hepatic damage, particularly the latter, are contraindications. It may be administered by the open drop, semi-open drop or closed machine method with soda lime absorption technic. The open drop method is preferable for short anesthesia. Adequate oxygen or air supply and an unobstructed airway are essential.

Caution—Vinyl ether is flammable and deteriorates on exposure to air and light. It must be preserved in tight containers of not more than 200 cc capacity and is not to be used if the original container has been open longer than 48 hours.

SHARP & DOHME, DIVISION OF MERCK & Co., INC.

Vinethene: 10, 25, 50 and 75 cc bottles. Packaged with plastic dropper.

U. S. patents 2,044,800, 2,044,801 and 2,099,695. U. S. trademark 312,453.

LOCAL ANESTHETICS

Methods of producing local anesthesia (that confined to a restricted area) vary with the site of application and the technic of administration. Certain drugs (e.g., cocaine, tetracaine) are effective in topical application to mucous membranes, for surface anesthesia.

Rarely used today are agents that produce freezing temperature to lower sensibility to pain (ethyl chloride, solid carbon dioxide) and protoplasmic poisons (phenol).

Local anesthesia produced by injectable compounds is designated according to the technic or anatomic site. Infiltration is injection directly into the area that is painful or subjected to surgical trauma, or nerve block injection in proximity to specific nerve trunks supplying a particular anatomic site. Particular block injections are designated according to the point chosen for interruption of nerve transmission. Two of these are: *spinal* (within the dural membrane surrounding the spinal cord and nerve roots), and *extra dural* or *epidural* (solutions deposited immediately outside the dural membrane, and within the bony spinal or caudal canals). Other blocks are designated according to their location along the course of nerve trunks on their way to the peripheral tissues.

To combat the vasodepressor effects of the local anesthetics, especially when they are injected centrally (spinal or epidural) long-acting vasoconstrictor agents (e.g., ephedrine) may be injected intramuscularly or intravenously for their systemic effect.

Certain local anesthetics cause vasoconstriction in the area applied (cocaine), others do not (tetracaine). For topical application and injection, epinephrine (or a similar less toxic vasoconstrictor agent, e.g., phenylephrine) usually is added in the preparation of solutions to impede rapid systemic absorption. Concentration of such agents in solutions to be injected should be kept at the minimum effective level (usually from 1 part in 130,000 to 1 part in 520,000 in the case of epinephrine). (See sympathomimetic agents in the chapter on autonomic drugs.)

The technical details of preparation and control of solutions to be injected, especially within the subdural or epidural spaces, are intricate and exacting. They should be acquired from authoritative source books and from instruction by experienced anesthetists. Details of dosage of any local anesthetic should be modified for different applications.

All local anesthetic agents are toxic and the tolerance of patients varies. Safe dosage, therefore, is limited for each drug, and administration must be individualized. Choice of drug, concentration, rate and location of injection, along with age, emotional and physical status of the patient, are a few of the factors involved. *One should use the smallest amount of the least toxic drug that will serve the purpose, if reactions are to be avoided.* The use of barbituric acid derivatives as premedication is advisable to prevent or decrease toxic reactions.

Accidental vascular injections are relatively frequent even in the practice of the most skillful anesthetist. Extreme caution also is imperative when any local anesthetic is applied under conditions in which trauma to mucous membrane is likely to occur. Hence, when local anesthetic drugs are being used, it is in the interest of safety to have instantly available (a) oxygen and the means of inflating the lungs with it and (b) a quick-acting barbituric acid compound prepared for intravenous administration. Local anesthetic solutions are too dangerous to be applied to the traumatized

urethra; general or spinal anesthetics should be employed. Lidocaine 1 per cent, lidocaine gel and piperocaine have been instilled into the urethra and bladder with good results, but such use of these drugs must be undertaken with extreme caution.

A special dosage form of local anesthetic solutions rendered hyperbaric by addition of dextrose may be employed in low spinal or saddle block anesthesia. As the solution is heavier than spinal fluid it tends to sink to the most dependent portion of the spinal canal. The technic of administration must take this characteristic into consideration since prolonged pooling of these concentrated solutions of anesthetics may cause extensive nerve damage. This may be avoided by proper timing in the positioning of the patient. Low spinal or saddle block anesthesia is of value in obstetrics for vaginal deliveries, in rectal surgery and in genito-urinary procedures not involving abdominal surgery.

A special dosage form of local anesthetic may be used to induce continuous caudal analgesia in obstetric cases. *The procedure must be undertaken only by skilled specialists and carried out with great caution because there is great danger of infection.* Two techniques have been used, one involves the use of a special malleable needle, the other a ureteral catheter. When the special needle is used, great care must be taken that the portion of the needle that lies outside the skin is protected, so that movement of the patient will not force the needle up into the caudal canal, against bone or into a blood vessel or dura. The patient should lie on her side. The needle must be protected against breakage. If it breaks within the canal, it must be removed within a few hours.

If a urethral catheter is to be employed, entry into the caudal canal should be made with a needle no larger than 15 gauge. If it is necessary to use a needle as large as 13 gauge and the caudal canal is not entered on the first attempt, the method should be discarded; otherwise infection is almost certain to occur. Extreme care must be exercised to prevent infection, one of the great dan-

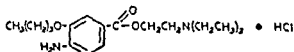
Continuous caudal analgesia is contraindicated in the presence of placenta praevia, inertia uteri, uncontrollable hysteria, anomalies of the sacrum and disproportion of child and pelvis. History of sensitivity to local anesthetics is another contraindication. Continuous caudal anesthesia is not suitable for difficult forceps rotation or version because in such cases complete relaxation of the uterus is imperative.

The slight solubility of some of these anesthetics renders them unsuitable for injection, but their slow absorption renders them safer, especially for ulcers, wounds and mucous surfaces. The anesthesia that they induce usually is not so complete as that induced by the soluble local anesthetics, but it is more lasting. They are practically nonirritant and nontoxic. Ethyl aminobenzoate (benzocaine, anesthesin) and orthoform are about equally effective through

intact mucous membranes; butyl aminobenzoate (butesin) is more effective than either.

Many, if not all, local anesthetics occasionally give rise to dermatitis. When this is severe, the use of the anesthetic should be discontinued.

BENOXINATE HYDROCHLORIDE.—Dorsacaine Hydrochloride (SMITH-DORSEY) — β -Diethylaminoethyl 4-amino-3-n-butoxybenzoate hydrochloride.—The structural formula of benoxinate hydrochloride may be represented as follows:



Physical Properties.—Benoxinate hydrochloride is a white, odorless, crystalline powder, with a melting point between 157 and 160°. It is freely soluble in alcohol, chloroform and water but insoluble in ether. Benoxinate hydrochloride is stable to air, heat and light. The pH of an aqueous solution is between 4.5 and 5.2.

Actions and Uses.—Benoxinate hydrochloride, a benzoic acid ester related to procaine, is an effective surface anesthetic agent useful in ophthalmology. It also has bacteriostatic properties. When applied locally to the conjunctiva and cornea, it produces slightly more intense anesthetic effect and is less irritating to the conjunctiva than comparable concentrations of tetracaine hydrochloride. A single instillation of 0.08 cc. of a 0.4 per cent solution produces, within 60 seconds, a sufficient degree of anesthesia to permit tonometry or, after three drops at 90-second intervals, removal of a foreign body embedded in the corneal epithelium. However, a decrease in the depth of anesthesia is noted after 20 to 30 minutes, and the sensitivity of the cornea returns to normal within 1 hour. This relatively short duration of anesthesia reduces the risk of exposure keratitis in minor procedures not requiring an eye bandage. The same instillation produces little conjunctival irritation; in most patients there is no visible hyperemia, increased winking or lacrimation. Instillations up to 0.5 cc. of a 0.4 per cent solution do not produce any measurable alteration in the size of the pupil or its reaction to light, nor is accommodation affected. Large single doses of 1 cc. of the 0.4 per cent concentration do not produce symptoms suggestive of systemic action.

Benoxinate hydrochloride is useful for tonometry, gonioscopy, removal of corneal foreign bodies and for short operative procedures involving the cornea and conjunctiva.

Benoxinate hydrochloride and tetracaine have about the same toxicity index when compared with cocaine, given as an intravenous injection in experimental animals. Clinically, no signs of local or systemic hypersensitivity have followed its prolonged use in the eye; it has been tolerated by some patients with a history of sensitivity to other commonly employed local anesthetic agents. Nevertheless, it should be employed with the usual precautions for surface anesthesia, and should be used sparingly in patients with

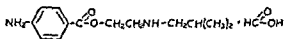
known allergies, cardiac disease, hyperthyroidism or open lesions

Dosage.—Benoxinate hydrochloride is administered only by topical instillation in the eye. One drop of a 0.4 per cent solution, well instilled, usually is adequate for tonometry, a second drop invariably permits measurement of ocular tension and insertion of a contact lens without delay. Within 4 to 5 minutes, three single drop instillations at 90-second intervals usually ensure adequate surface anesthesia for removal of an embedded foreign body in the cornea or for opening a chalazion through the conjunctival surface.

SMITH-DORSEY, DIVISION OF THE WANDER COMPANY

Solution Dorsecaine Hydrochloride 0.4%.—15 cc plastic dropper bottles. An isotonic solution containing 4 mg of benoxinate hydrochloride in each cubic centimeter. Preserved with 0.02 per cent butyl *p*-hydroxybenzoate.

BUTETHAMINE FORMATE.—Monocaine Formate (NOVOCOL)—2-Isobutylaminoethyl *p*-aminobenzoate formate.—The formic acid salt of the ester formed from *p*-aminobenzoic acid and the *N*-isobutyl derivative of ethanolamine. The structural formula of butethamine formate may be represented as follows:



Physical Properties.—Butethamine formate forms odorless, white crystals, which melt between 136 and 139°. It is freely soluble in alcohol and water, very slightly soluble in benzene and slightly soluble in chloroform and ether. The pH of a 1 per cent solution is about 6.1.

Actions and Uses.—Butethamine formate is proposed for use in spinal anesthesia. Its action is qualitatively identical with that of procaine, but it produces about one-third greater anesthetic and toxic effects.

Dosage.—For spinal anesthesia the dosage depends on the speed

NOVOCOL CHEMICAL MFG. COMPANY, INC.

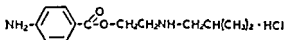
Crystals Monocaine Formate: 50, 100, 150 and 200 mg ampuls; 300 and 500 mg containers (fractional doses). For spinal anesthesia

Solution Monocaine Formate 5%: 2 cc. ampuls. A solution in sterile distilled water containing 50 mg of butethamine formate in each cubic centimeter. For spinal anesthesia.

U S patent 2,139,818 U S trademark 353,653

BUTETHAMINE HYDROCHLORIDE-N.F.—Monocaine Hydrochloride (NOVOCOL)—2-Isobutylaminoethyl-*p*-aminobenzoate hydro-

chloride.—"Butethamine Hydrochloride, dried at 105° for 2 hours, yields not less than 98.5 per cent of $C_{13}H_{20}N_2O_2 \cdot HCl$." *N.F.* The structural formula of butethamine hydrochloride may be represented as follows:



Physical Properties.—Butethamine hydrochloride is a white, odorless, crystalline powder with a bitter taste and anesthetizing effects. It melts between 192 and 196°. It is sparingly soluble in water, slightly soluble in alcohol and chloroform, very slightly soluble in benzene and practically insoluble in ether. The pH of a 1 per cent solution is about 4.7.

Actions and Uses.—Butethamine hydrochloride is a local anesthetic similar to procaine hydrochloride. It is used for nerve block anesthesia in dentistry and other surgery. Present evidence does not warrant its use for topical or surface anesthesia of mucous or other membranes. Its effects, either with or without the addition of epinephrine hydrochloride, are qualitatively identical with those of procaine. Quantitatively, butethamine hydrochloride has about one-third more anesthetic and toxic potency than procaine (i.e., a butethamine hydrochloride solution of three-fourths the concentration of a procaine solution is of equal effectiveness).

Dosage.—For dental or other minor surgery, a 1 per cent solution with epinephrine 1:75,000 may be injected to obtain nerve block anesthesia. In major surgery or other procedures requiring nerve block anesthesia equivalent to that produced by 2 per cent procaine, a 1.5 per cent solution of butethamine hydrochloride with epinephrine 1:100,000 may be used. (See caution under the general statement on local anesthetics.)

NOVOCOL CHEMICAL MFG. COMPANY, INC.

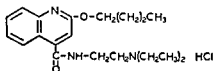
Solution Monocaine Hydrochloride 1% with Epinephrine 1:75,000: 2, 3 and 5 cc ampuls, 2, 2.5 and 5 cc Anestubes (syringe cartridge), 2.5 and 5 cc Novampuls (ampul type syringe); and 30, 60 and 120 cc. bottles. A solution in sterile distilled water containing 10 mg. of butethamine hydrochloride, 0.01 mg. of epinephrine, 1.5 mg. of sodium bisulfite, and 6.5 mg. of sodium chloride in each cubic centimeter.

Solution Monocaine Hydrochloride 1.5% with Epinephrine 1:100,000: 2, 3 and 5 cc ampuls, 1, 2, 2.5 and 5 cc Anestubes (syringe cartridge), 2.5 and 5 cc Novampuls (ampul type syringe); 60 and 120 cc. bottles. A solution in sterile distilled water containing 15 mg. of butethamine hydrochloride, 0.01 mg. of epinephrine, 1.5 mg. of sodium bisulfite, and 4.5 mg. of sodium chloride in each cubic centimeter.

U. S. patent 2,139,818 U. S. trademark 353,653

DIBUCAINE HYDROCHLORIDE-U.S.P.—Nupercaine Hydrochloride (CIBA).—2-Butoxy-n-(2-diethylaminoethyl)cinchoninamide

hydrochloride.—The structural formula of dibucaine hydrochloride may be represented as follows



Physical Properties.—Dibucaine hydrochloride occurs as fine, white, lustrous crystals or as a white powder. It is odorless and quite hygroscopic. It exhibits a bitter, acrid taste with a prolonged local anesthetic action and is sensitive to light. One gram of dibucaine hydrochloride dissolves in about 2 cc of water. It is freely soluble in alcohol, in acetone and in chloroform but only slightly soluble in cold benzene, in ethyl acetate and in toluene.

Actions and Uses.—Dibucaine hydrochloride is a local anesthetic that acts like cocaine when applied to mucous surfaces and like procaine or cocaine when injected, the action being prolonged. Dibucaine hydrochloride is about five times as toxic as cocaine when it is injected intravenously into animals, and its anesthetic activity is correspondingly greater than that of cocaine when it is applied to a mucous surface, injected subcutaneously it is many times more active than procaine hydrochloride. It has caused

tion

A 1.400 solution of dibucaine hydrochloride made hyperbaric with 5 per cent of dextrose may be used for low spinal or saddle block anesthesia.

Warning. Pooling of this concentrated solution of dibucaine hydrochloride in the conus may cause extensive nerve damage. Therefore, the patient should not be kept in the sitting position for more than 1 minute following the introduction of the agent into the spinal canal.

Dosage.—An 0.25 per cent solution made hyperbaric with 5 per

caution in the general statement on local anesthetics.)

Other dosage forms of this drug have been exempted and were last described in *N.N.R.* 1952.

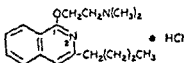
CIBA PHARMACEUTICAL PRODUCTS, INC.

Heavy Solution Nupercaine Hydrochloride with Dextrose: 2 cc.

ampuls. A solution containing 2.5 mg. of dibucaine hydrochloride and 50 mg. of dextrose in each cubic centimeter.

U. S. patent 1,825,623 U. S. trademark 266,366.

DIMETHISOQUIN HYDROCHLORIDE.—*Quotane Hydrochloride* (SMITH, KLINE & FRENCH) —3-Butyl-1-(2-dimethylaminoethoxy)-isoquinoline hydrochloride.—The structural formula of dimethisoquin hydrochloride may be represented as follows:



Physical Properties.—Dimethisoquin hydrochloride is a white powder with a bitter, numbing taste and a slight aromatic odor, with a melting point between 144 and 147°. It is freely soluble in alcohol and very slightly soluble in ether. The approximate amount that dissolves at 25° in 100 cc. of water is 5 Gm. The pH of a 1 per cent solution is between 3.5 and 5.0.

Actions and Uses.—Dimethisoquin hydrochloride, an active surface anesthetic, differs chemically from local anesthetics of the benzoate ester type, such as procaine, and is somewhat more active. Its toxicity is less than that of dibucaine but greater than that of cocaine or procaine. Its index of sensitization is considered to be somewhat less than that of procaine derivatives.

Dimethisoquin hydrochloride is useful topically for the relief of

greater than that of the vehicle in which it is applied. It also may reduce the pain of sutured surgical wounds. Because of its apparent lack of systemic toxicity and low index of sensitization when applied to the skin, the drug is considered relatively safe for unsupervised use as a topical remedy for symptomatic relief of simple irritations that may accompany undiagnosed minor skin conditions. When these symptoms persist, the underlying cause should be determined by consultation with a physician. Relief of pruritus also may aid in the treatment of the underlying cause with more specific forms of therapy.

Although dimethisoquin hydrochloride has not been associated with systemic toxicity or sensitivity when applied topically to mucous membranes, its use should be restricted to the skin until there has been longer experience regarding its effects on other tissues. For the same reason it should not be applied to extensive areas of the skin. Contact with the eyes should be avoided to prevent stinging.

Dosage.—Dimethisoquin hydrochloride is applied topically to the skin, either as a 0.5 per cent lotion for moist lesions, or as a 0.5 per cent ointment for dry lesions. Either lotion or ointment is applied as a thin film over the affected area. One application of either form usually provides relief for 2 to 4 hours. Application

more than four or five times daily seldom is required. Should sensitization appear after repeated applications, further use should be discontinued.

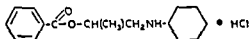
SMITH, KLINE & FRENCH LABORATORIES

Lotion Quotane Hydrochloride 0.5%: 60 cc bottles. An oil-in-water emulsion containing 5 mg of dimethisoquin hydrochloride in each gram Preserved with 0.1 per cent propylparaben and 0.15 per cent ethylparaben

Ointment Quotane Hydrochloride 0.5%: 28.4 Gm tubes An ointment containing 5 mg of dimethisoquin hydrochloride in each gram Preserved with 0.2 per cent thimerosal

U S patent 2,612,503 U S trademark 557,670

HEXYLCAINE HYDROCHLORIDE.—Cyclaine Hydrochloride (SHARP & DOHME) —1-Cyclohexylamino-2-propyl benzoate hydrochloride—The structural formula of hexylcaine hydrochloride may be represented as follows.



Physical Properties.—Hexylcaine hydrochloride is a white, bitter powder with a slight aromatic odor, and with a melting point between 182 and 184°. It is freely soluble in alcohol and in chloroform and practically insoluble in ether. The approximate amount that dissolves at 25° in water to form 100 cc. of solution is 6 Gm. The pH of a 5 per cent solution is between 4.1 and 4.7.

Actions and Uses.—Hexylcaine hydrochloride is a soluble local

anesthetic. It is used for infiltration anesthesia and for surface anesthesia. It is also used for the treatment of neuralgia and for the relief of pain in the treatment of burns and scalds. It is also used for the treatment of the following conditions:—

and that, from the standpoint of duration of anesthesia and degree of motor paralysis produced, it compares favorably with equal concentrations of the more active local anesthetic compounds in use. When applied topically, it is at least as potent as equal concentrations of cocaine. Clinical studies also indicate that, when used for infiltration and nerve block, it is faster and longer acting than an equal concentration of procaine.

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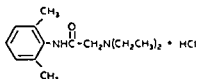
Dosage.—Hexylcaine hydrochloride should be administered in the smallest dose that will give the required anesthesia.

For infiltration anesthesia to relieve local pain, 5 to 65 cc. of a 1 per cent solution is injected into the affected area.

cubic centimeter. Preserved with 0.15 per cent methylparaben and 0.02 per cent propylparaben.

U. S. patent 2,486,374 U. S. trademark 426,983

LIDOCAINE HYDROCHLORIDE.—Xylocaine Hydrochloride (ASTRA)— α -Diethylamino-2,6-acetoxylidide hydrochloride—Lidocaine hydrochloride is prepared in solution by the action of hydrochloric acid with lidocaine-NF. The structural formula of lidocaine hydrochloride may be represented as follows:



Physical Properties.—The base lidocaine is a white, crystalline solid with a characteristic odor. It is very soluble in alcohol and chloroform, freely soluble in benzene and ether and practically insoluble in water.

Actions and Uses.—Injection of lidocaine hydrochloride, a potent local anesthetic agent, produces more prompt, intense and extensive anesthesia than an equal concentration of procaine hydrochloride. Its anesthetic potency and the area of anesthesia are approximately twice those of procaine. When the concentration is 0.5 per cent, the duration of anesthesia is about the same as that of procaine. When the concentration is 1 per cent, its toxicity exceeds that of procaine hydrochloride; at 1 per cent, it is 40 per cent greater, at 2 per cent, 50 per cent greater. It is compatible with epinephrine hydrochloride, with which it may be combined to delay absorption, prolong action and reduce its toxic effects. It is also used without epinephrine when vasopressor drugs are contraindicated. Systemic side reactions and local irritant effects are rare. Nausea and vomiting, muscular twitching and chilling have been observed.

The onset of anesthesia is rapid, usually within 1 to 2 minutes, and the effect is of long duration, usually 1 to 2 hours.

It is used for the anesthesia of the oral cavity, the peritoneal cavity during surgery or instrumentation. The onset of mucosal anesthesia may be delayed as much as 5 minutes, and, depending on the amount employed, the anesthesia persists for 1 to 2 hours.

by these routes with lower dosage.

Dosage.—Lidocaine hydrochloride is injected according to the type of local anesthesia to be induced. The total dosage injected in 24 hours should not exceed 0.5 Gm. per patient when used with

epinephrine; without epinephrine, the total dosage should be proportionately less. The maximum safe total dosage also may vary in accordance with the influence of other conditions existing at the time of injection of any particular individual.

Solutions of half the strength of those used in procaine anesthesia should provide equivalent anesthetic potency. It should be remembered that solutions containing more than 0.5 per cent of lidocaine hydrochloride are more toxic than similar concentrations of procaine hydrochloride.

For infiltration anesthesia the 0.5 per cent concentration with epinephrine hydrochloride 1:100,000 is ordinarily used, the volume injected depending on the extent of the area to be anesthetized. In minor surgery 2 to 50 cc of this solution is usually adequate, but in major surgery, up to 100 cc may be required. If larger amounts (up to 200 cc) are injected, as in thoracoplasty, the solution should be 0.25 per cent. For block anesthesia a 1 or 2 per cent concentration with epinephrine hydrochloride 1:100,000 is used, depending on the site and structures concerned. The 2 per cent concentration without epinephrine is suitable for block anesthesia of the digits. A 2 per cent solution with epinephrine 1:50,000 is used for certain odontologic procedures.

A 1 per cent solution is employed topically for mucosal anesthesia, it may be applied by means of cotton pledgets or applicators to the mucous membrane of the oral cavity or female urethra, to the peritoneum or, by injection, into the male urethra.

ASTRA PHARMACEUTICAL PRODUCTS, INC

Solution Xylocaine Hydrochloride 0.5%: 20 and 50 cc vials. A solution containing 5 mg of lidocaine hydrochloride and 8 mg. of sodium chloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

Solution Xylocaine Hydrochloride 0.5% with Epinephrine Hydrochloride 1:100,000: 20 and 50 cc. vials. A solution containing 5 mg. of lidocaine hydrochloride, 0.01 mg. of epinephrine hydrochloride, and 8 mg of sodium chloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

Solution Xylocaine Hydrochloride 1%: 20 and 50 cc vials. A solution containing 10 mg of lidocaine hydrochloride and 7 mg of sodium chloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

Solution Xylocaine Hydrochloride 1% with Epinephrine Hydrochloride 1:100,000. 20 and 50 cc vials. A solution containing 10 mg of lidocaine hydrochloride, 0.01 mg of epinephrine hydrochloride and 6 mg. of sodium chloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

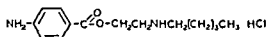
Solution Xylocaine Hydrochloride 2%: 20 and 50 cc. vials and 1.8 cc. cartridges. A solution containing 20 mg. of lidocaine hydrochloride and 6 mg. of sodium chloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

Solution Xylocaine Hydrochloride 2% with Epinephrine Hydrochloride 1:100,000; 20 and 50 cc. vials and 1.8 cc. cartridges. A solution containing 20 mg of lidocaine hydrochloride, 0.01 mg of epinephrine hydrochloride and 6 mg. of sodium chloride in each cubic centimeter Preserved with 0.1 per cent methylparaben.

Solution Xylocaine Hydrochloride 2% with Epinephrine Hydrochloride 1:100,000; 20 and 50 cc. vials and 1.8 cc. cartridges. A solution containing 20 mg of lidocaine hydrochloride, 0.01 mg of epinephrine hydrochloride and 6 mg. of sodium chloride in each cubic centimeter Preserved with 0.1 per cent methylparaben

U. S. patent 2,441,498. U. S. trademark 534,232

NAEPAINES HYDROCHLORIDE-N.F.—Amylsine Hydrochloride (Novocol) —2-Amylaminoethyl *p*-aminobenzoate hydrochloride—"Naepaine Hydrochloride, dried at 104° for 4 hours, yields not less than 98.5 per cent of $C_{14}H_{22}N_2O_2 \cdot HCl$ " *N.F.* The structural formula of naepaine hydrochloride may be represented as follows:



Physical Properties.—Naepaine hydrochloride is a fine, white, odorless powder which, when applied to the tongue, produces a bitter taste followed by a sense of numbness. It is soluble in water.

Actions and Uses.—The actions of naepaine hydrochloride resemble those of cocaine hydrochloride, but the solution does not cause mydriasis when dropped into the eye. Its use should be restricted to the production of corneal anesthesia in cases in which mydriasis is not desired. The toxicity varies widely with the species and with the mode of administration. The anesthesia is induced promptly with little smarting and the drug does not increase intraocular tension.

Dosage.—A 2 per cent or 4 per cent solution is used in ophthalmology when mydriasis is not desired, 1 or 2 drops usually being sufficient.

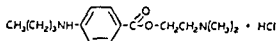
NOVOCOL CHEMICAL MFG. COMPANY, INC.

Powder Amylsine Hydrochloride: 5 Gm. vials and 28.3 Gm. bottles.

Solution Amylsine Hydrochloride 4%: 30 cc. bottles.

U. S. patent 2,139,818 (Dec. 13, 1938, expires 1953) U. S. trademark 404,009.

TETRACAINE HYDROCHLORIDE-U.S.P.—Pontocaine Hydrochloride (WINTHROP-STEARNs)—Amethocaine Hydrochloride.—2-Dimethylaminoethyl *p*-butylaminobenzoate hydrochloride.—“Tetracaine Hydrochloride contains not less than 98.5 per cent of $C_{15}H_{24}N_2O_2 \cdot HCl$, calculated on the dried basis.” *U.S.P.* The base of tetracaine hydrochloride differs from procaine base in that one of the hydrogens of the *p*-amino group is replaced by a butyl group, and the two ethyl groups of procaine are replaced by two methyl groups. The structural formula of tetracaine hydrochloride may be represented as follows



Physical Properties—Tetracaine hydrochloride occurs as a fine, white, crystalline, odorless powder. It has a slightly bitter taste followed by a sense of numbness. Its solutions are neutral to litmus paper. It is very soluble in water and soluble in alcohol. It is insoluble in ether and in benzene. It melts between 147 and 150°.

Actions and Uses—Tetracaine hydrochloride is a local anesthetic with actions similar to those of procaine hydrochloride, but when applied to mucous membranes it is effective in lower concentrations (See caution in the general statement on local anesthetics.) It is used for surface anesthesia in the eye, nose and throat, for prolonged spinal anesthesia and for continuous caudal analgesia.

Dosage.—Solution of tetracaine hydrochloride, 0.5 per cent is used in the eye; a 2 per cent solution is applied to the nose and throat. A 0.5 per cent solution is injected for spinal anesthesia, the dose being from 2 to 4 cc (from 10 to 20 mg. of the salt). A total of 20 mg. is considered the maximum safe dose for spinal injection.

For continuous caudal analgesia an initial skin wheal is raised with the local anesthetic and the underlying tissues infiltrated so that the needle may be inserted into the sacral canal without excessive discomfort to the patient. Thirty cubic centimeters of tetracaine hydrochloride 0.15 per cent solution is injected. Signs of fullness in one or both legs, progressive loss of painful sensations and relief of abdominal uterine cramps will occur in 5 to 15 minutes. Supplementary injections depend on the individual patient. Usually

agement of labor, delivery and repairs

Solutions of tetracaine hydrochloride, made hyperbaric with 6 per cent dextrose, are employed in a concentration of 0.2 per cent for the production of low spinal anesthesia by the saddle block technic in obstetric and perineal surgery and in a concentration of 0.3 per cent for low, median or high spinal anesthesia in general surgery; the single total dosage employed for such procedures should not exceed 6 mg.

WINTHROP-STEARNs, INC.

Ophthalmic Ointment Pontocaine Base: An ointment containing 0.5 per cent of tetracaine base, the free base of tetracaine hydrochloride, dissolved in white petrolatum.

Pontocaine Hydrochloride "Niphanoid": Ampuls containing 10, 15 or 20 mg of tetracaine hydrochloride. For spinal anesthesia.

Solution Pontocaine Hydrochloride: 100 cc bottles. An isotonic solution containing 15 mg of tetracaine hydrochloride in each cubic centimeter. For caudal anesthesia.

Solution Pontocaine Hydrochloride 0.2% with Dextrose 6%: 2 cc. ampuls. A hyperbaric solution containing 2 mg of tetracaine hydrochloride in each cubic centimeter. For saddle block anesthesia.

Solution Pontocaine Hydrochloride 0.3% with Dextrose 6%: 5 cc ampuls. A hyperbaric solution containing 3 mg of tetracaine hydrochloride in each cubic centimeter. For spinal anesthesia.

Solution Pontocaine Hydrochloride 0.5%: 15 and 60 cc bottles. Preserved with 0.4 per cent chlorobutanol.

Solution Pontocaine Hydrochloride 1%: 2 cc. ampuls. A solution containing 10 mg. of tetracaine hydrochloride, 6.6 mg of sodium chloride and 2 mg of acetone sodium bisulfite in each cubic centimeter.

Solution Pontocaine Hydrochloride 2%: 30 and 120 cc. bottles. Preserved with 0.4 per cent chlorobutanol. Tinted with methylene blue to prevent accidental use for injection.

Tablets Pontocaine Hydrochloride: 0.1 Gm. Each tablet contains 0.1 Gm of tetracaine hydrochloride, 5 mg of boric acid and not more than 0.5 mg of acetone sodium bisulfite. To be used only for preparing solutions for surface anesthesia (not for injection) in rhinolaryngology, ophthalmology and dentistry.

U S trademark 282,418.

Local Anti-infectives

ANTIBACTERIAL AGENTS

The drugs included in this chapter are antibacterial, antifungal and antiparasitic agents. Agents of these classes that are administered internally (orally or parenterally), though employed for their local action, are described in the chapter on systemic anti-infectives. The antibacterials include disinfectants and antiseptics. Disinfectants usually are chemical substances that destroy disease germs or other

spores.

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septic thus prevents sepsis, putrefaction or decay. It is obvious that no sharp distinction can be drawn between disinfectants and antiseptics.

The ideal disinfectant or antiseptic may never be discovered. Such a substance must possess the ability to destroy all forms of all infectious agents without being toxic to human tissue cells or inducing sensitization. It would need to be capable of penetrating tissue and of acting in the presence of organic matter such as body fluids. It would need to be soluble, stable, noncorrosive and inexpensive.

Because various infectious agents differ chemically, they naturally vary in their susceptibility to the different types of chemical substances employed for anti-infectives. Thus, it is necessary to select the anti-infective best suited to accomplish the desired results.

Criteria for the evaluation of disinfectants and antiseptics are not well established. The incorporation of "inactivators" in both *in vitro* and *in vivo* tests of the bactericidal and bacteriostatic properties of antibacterial agents undoubtedly will aid in establishing their efficacies. Unfortunately, adequate neutralizers for all of the active compounds included in antibacterial agents have not yet been discovered.

For the Council's requirements for the acceptance of disinfectants and antiseptics, see the section in the rules on evaluation of certain products.

Antibiotics

Antibiotics are chemical substances of microbial origin that inhibit the growth of the metabolic activities of bacteria or other micro-organisms. A given antibiotic may be produced by several

may possess broad range of infectious agents and that they do not induce the development of drug-resistant strains of infectious agents that are of the thousands of antibiotics number of them possess the ability to be used as anti-infectives; some may be primarily bacteriostatic; some may be bactericidal as well as bacteriostatic. In some cases bacteriolysis may occur. Some antibiotics that are too toxic to be employed parenterally, such as tyrothricin, may be employed topically.

TYROTHRINICIN-U.S.P.—Soluthricin (SHARP & DOHME)—“Tyrothricin is an anti-bacterial substance produced by the growth of *Bacillus brevis* Dubos (Fam. *Bacteriaceae*). It consists principally of gramicidin and tyrocidine, the tyrocidine usually being present as the hydrochloride.

“Tyrothricin has a potency of not less than 90 per cent of the U.S.P. Tyrothricin Reference Standard.” U.S.P.

Physical Properties.—Tyrothricin occurs as a white to buff-colored powder. It is soluble in alcohol, acetone and dioxane; insoluble in water, chloroform and ether. It is resistant to the action of pepsin and trypsin. Heat and exposure to proteolytic enzymes render it insoluble in neutral buffer solutions.

gr
pc
ba

mixture Tyrothricin is active primarily against the gram-positive micro-organisms. These include species of pneumococci, streptococci and staphylococci. Tyrothricin inhibits enzymatic action, retards growth and causes lysis of susceptible bacteria.

Tyrothricin is ineffective when administered orally and ineffective and dangerous when given intravenously.

It may be used with caution in body cavities as long as there is no direct connection with the blood stream. But in no instance should proper surgical treatment be omitted. It has been of value in the treatment of superficial indolent ulcers where the predominating organism is gram-positive, and in mastoiditis, empyema and some other wound infections. Its field of usefulness is limited and it exerts no effect unless it comes in direct contact with the organisms. Thus, it may not be effective in the presence of deep-seated infections. Body fluids, such as saliva, urine and serum, inhibit action slightly, whereas substances from gram-negative organisms are decidedly inhibiting.

Indiscriminate use of tyrothricin solutions for irrigation of the paranasal sinuses or other cavities close to the subarachnoid space following surgery should be avoided because of the danger of chemical meningitis.

Dosage.—Tyrothricin must be applied locally, *not intravenously or by mouth*. It is administered after dilution with sterile distilled water to form an isotonic solution that yields 500 mcg. of the drug per cubic centimeter. This concentration usually is effective. Higher concentrations may be used if indicated but may irritate the tissues.

PARKE, DAVIS & COMPANY

Solution Tyrothricin 2%: 10 and 50 cc. vials. A 92 per cent alcoholic solution containing 20 mg. of tyrothricin in each cubic centimeter.

S. B. PENICK & COMPANY

Solution Tyrothricin 4%: 200 and 500 cc. vials. A 23 per cent alcoholic solution containing 40 mg. of tyrothricin in each cubic centimeter.

Tyrothricin: Bulk 100, 500 and 1,000 Gm glass jars.

SHARP & DOHME, DIVISION OF MERCK & Co., INC.

Solution Soluthricin 0.05%: 240 cc. bottles. A solution in 1 per cent alcohol, propylene glycol and water containing 0.5 mg. of tyrothricin and 0.2 mg. of cetyldimethylethylammonium bromide in each cubic centimeter.

Solution Soluthricin (*Concentrate*) 2.5%: 10 and 20 cc. vials. A solution in 50 per cent alcohol and propylene glycol containing 25 mg. of tyrothricin and 10 mg. of cetyldimethylethylammonium bromide in each cubic centimeter.

U. S. trademark 421,710

Halogen Compounds

Chlorine Derivatives

Chlorine is the most widely used and one of the most reliable of all chemical disinfectants. Labarraque introduced chlorinated lime as a disinfectant in the French catgut industry in 1829, subsequently, chlorine has been utilized primarily in sanitation engineering, for the disinfection of drinking water and swimming pools, and in surgery and obstetrics.

The disinfecting action of chlorine compounds depends on the free chlorine liberated or on the vigorous oxidizing action resulting from their decomposition. Its efficiency is reduced greatly by the presence of organic matter, due to its affinity for the protein molecule. It replaces the hydrogen in the alpha-amino groups of the protein molecule to form unstable chloramino acids. For this reason, frequent application of fresh chlorine preparations to wounds is necessary.

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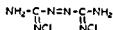
hypochlorite solution is both stable and rapidly germicidal. Mixtures of sodium hypochlorite and calcium hypochlorite have the advantages of stability and moderate alkalinity and, therefore, are less caustic. Germicidal efficiency of these solutions requires a maximum of available chlorine in the form of hypochlorous acid. Hypochlorite preparations such as Dakin's solution, in concentrations that are germicidally effective, tend to devitalize tissues and digest blood clots. They have been superseded by less toxic medicaments

chlorites and exert antibacterial action more slowly. Chloramines are more stable and less irritating to tissue than are hypochlorite solutions of similar strength.

Chlorine is relatively unselective toward micro-organisms. Pathogens of the colon-typhoid group and many of the pathogenic spores are sensitive to its action, *Mycobacterium tuberculosis* resists destruction by chlorine. Filterable viruses are inactivated by chlorine, but it is doubtful that the concentration ordinarily employed in drinking water is sufficient to insure their destruction.

In general, increase in temperature and acidity increases germicidal activity of chlorine and chlorine compounds.

CHLOROAZODIN N.F.—Azochloramid (WALLACE & TILNAN)— α, α' -Azobis(chloroformamidine)—"Chloroazodin contains not less than 97 per cent and not more than 102 per cent of $C_2H_4Cl_2N_6$ " N.F. The structural formula of chloroazodin may be represented as follows



Physical Properties.—Chloroazodin occurs as bright, yellow needles or flakes. It has a faint odor suggestive of chlorine and a slightly burning taste. Solutions of chloroazodin in glycerin and in alcohol decompose rapidly on warming, and all solutions of chloroazodin decompose on exposure to light. Chloroazodin decomposes explosively at about 155° . Its decomposition is accelerated by contact with metals. It is very slightly soluble in water, sparingly soluble in alcohol, slightly soluble in glycerin and in glyceryl triacetate and very slightly soluble in chloroform.

Actions and Uses.—The actions and uses of chloroazodin are similar to those of a dilute solution of sodium hypochlorite and the other chloramines. However, it does not hydrolyze appreciably in aqueous solutions and it has a low rate of reaction with mild reducing agents and other organic matter. Consequently, its

tion of
pH 7.4 ;
mucous

solution buffered at
proposed for use on
the stable solution

of 1.500 in glyceryl triacetate (triacetin) is used. Gauze impregnated with the triacetin solution of chloroazodin does not dry out or stick to the wound. A solution prepared by mixing 1 volume of a strong solution of chloroazodin in triacetin (1:125) with 19 volumes of a vegetable oil contains 1 part of chloroazodin in 2,000 parts (by weight) of the solution and is sufficiently bland to be applicable to mucous membranes of the vagina, colon and rectum.

WALLACE & TIERNAN, INC

Powder Saline Mixture of Azochloramid. Bottles of the powder containing 36 Gm. for preparing 1 gallon of aqueous solution of chloroazodin (1:3,300) contain 3.2 per cent chloroazodin, 89.6 per cent sodium chloride, 1 per cent monopotassium phosphate and 6.3 per cent anhydrous sodium phosphate by weight.

Solution Azochloramid in Triacetin (1:500): 59, 236 and 946 cc. and 3.78 liter containers. A solution containing 1 Gm. chloroazodin in 500 Gm. of triacetin. Triacetin is a mixture of glyceryl acetates containing approximately 95 per cent of glyceryl triacetate.

Strong Solution Azochloramid in Triacetin (1:125). 50 cc. bottles. A solution containing 1 Gm. chloroazodin in 125 Gm. triacetin for use in the preparation of chloroazodin in vegetable oil (1:2,000)

Tablets Saline Mixture of Azochloramid. Each tablet contains 18 mg. of chloroazodin in buffered saline mixture for the preparation of 60 cc. of aqueous solution (1:3,300)

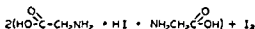
U. S. trademark J22,242.

Iodine and Derivatives

Certain iodine compounds are used for their local irritant and antiseptic effects, which are due probably to the action of free iodine contained in the preparations or liberated from them; or they may be administered for their systemic actions and for roentgen-ray diagnosis.

Iodine is one of the most efficient chemical bactericides in current usage. Its germicidal action does not vary greatly for the vegetative forms of various species of micro-organisms, it is effective over a wide pH range, and it is effective against spores. Its action is rapid and is principally bactericidal rather than bacteriostatic. The tincture of iodine formerly containing 7 per cent iodine and 5 per cent potassium iodide was excessively strong and has been replaced by 2 per cent iodine tincture-U.S.P. The alcohol in the tincture is irritating to open wounds and is not essential for the

antibacterial action. To obviate this undesirable feature a 2 per cent iodine solution-N.F. is available.



Physical Properties.—Diglycocoll hydroiodide-iodine is a dark, almost black, lumpy powder with a strong odor of iodine. It is freely soluble in water and practically insoluble in chloroform. Although it is only very slightly soluble in alcohol, the iodine component is soluble. The pH of a 0.1 per cent solution of digly-

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ers

Amounts of the preparation sufficient for disinfection of water are well below the toxic level. It produces a slight iodine taste and color that are reasonably tolerable. Its advantage over simple iodine solutions for the disinfection of water is its dry, stable form.

two tablets should be used per liter of water. The highest iodine

chlorine demand

The tablets should be protected against moisture from the air, but are otherwise stable and maintain effectiveness for 3 months even under conditions involving a temperature of 140° F.

Water on the lips of containers in which disinfection is carried out does not come in contact with the iodine or form a part of the

measured portion being disinfected; therefore, these should not be used as drinking receptacles until the treated portion has been allowed to run across such areas to eliminate all untreated water.

BURNHAM SOLUBLE IODINE COMPANY

Tablets Bursoline: Each tablet contains 8.2 mg. of iodine, 18 mg. of diglycine hydroiodide and 88.8 mg. of sodium acid pyrophosphate.

U. S. trademark 422,297.

Metal Compounds

Mercury

The antibacterial action of compounds of mercury is principally bacteriostatic. Their activity is greatly diminished in the presence of serum and other proteins, and they cannot be relied upon to kill spores. Because of their bacteriostatic action, solutions of mercury compounds with dyes or other organic radicals are used for antiseptics of the skin. These organic compounds of mercury are less toxic and less irritating than the older chlorides, iodides and cyanides of mercury. Their ability to penetrate deeply into living tissue has not been established.

The antibacterial action of the mercurial compounds appears to be due to the inactivation of essential enzymes by a reversible reaction with sulphydryl groups.

The organic mercurials frequently are used as preservatives. The germicidal action of tinctures of the organic mercurials often is due to the alcoholic menstruum in which they are dissolved.

Phenylmercuric chloride and basic phenylmercuric nitrate were found to possess antibacterial activity against certain organisms. The phenylmercuric ion of such compounds, the active mercuric ion, the structure of which is as follows:



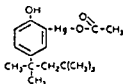
iodides and soaps react with phenylmercuric ion to precipitate a phenylmercuric salt. The extent of precipitation depends on the nature and the concentration of the supplanting salts.

The phenylmercuric ion (C_6H_5Hg)⁺ is more stable in acid than in alkaline solutions of its salts. Aqueous solutions containing phenylmercuric ions, buffered with inorganic or organic acids, are fairly stable. In the presence of organic solvents the stability is

other than aluminum, except as these properties may be influenced by the particular acid employed. Solutions of phenylmercuric salts may develop increasing amounts of mercuric and mercurous ions or free mercury as the result of gradual decomposition of phenylmercuric ions.

Phenylmercuric compounds are active against a variety of pathogenic bacteria and of relatively low toxicity to human tissue. Like other types of organic mercurial antiseptics, however, they cannot be depended on to kill bacterial spores. The presence of buffered solutions of phenylmercuric salts does not interfere with the precipitin reaction of human serum, the action of complement, the digestive action of pepsin and trypsin or the antigenic power of vaccine. Despite their low toxicity, phenylmercuric compounds may produce irritation, "burns" or poisoning in occasional individuals with undue sensitivity. In rabbits the minimum lethal intravenous dose of a 0.067 per cent (1:1,500) aqueous solution of basic phenylmercuric nitrate (buffered with 0.1 per cent boric acid) is 7 cc. per kilogram of body weight. The minimum lethal oral dose for these animals is approximately three times the intravenous dose. The toxicity of solutions of this and other phenylmercuric salts varies according to the concentration of phenylmercuric ions, the presence of organic solvents, the acid that is added as a buffer to render them stable and the degree of decomposition. The appearance of metallic mercury as a precipitate in solutions of phenylmercuric salts indicates extensive decomposition.

ACETOMEROCTOL.—Merbak (SCHIEFFELIN).—2-Acetoxymercuri-4-(1,1,3,3-tetramethylbutyl)phenol.—The structural formula of acetomerocetol may be represented as follows:



Physical Properties.—Acetomerocetol is a white solid which melts between 155 and 157°. It is freely soluble in alcohol, soluble in ether and chloroform, sparingly soluble in benzene and practically insoluble in water.

Actions and Uses.—Acetomerocetol, an organomercurial, is employed as a topical antiseptic for the prevention and control of

superficial infection. It is subject to the same limitations of usefulness as other organic mercurial antiseptics. The alcohol-acetone solution accounts for a significant part of the antibacterial action of the preparation. These components may produce irritation when used on mucous membranes or extensive superficial wounds.

Dosage.—Acetomerocetol is applied locally in 1:1,000 solution containing 50 per cent alcohol and 10 per cent acetone.

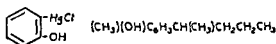
SCHIEFFELIN & COMPANY

Tincture Merbak 1:1,000 (Colored): 30, 118 and 473 cc. and 3.78 liter bottles. A solution of 50 per cent alcohol and 10 per cent acetone containing 1 mg acetomerocetol in each cubic centimeter.

Tincture Merbak 1:1,000 (Stainless): 118 and 473 cc. and 3.78 liter bottles. A solution of 50 per cent alcohol and 10 per cent acetone containing 1 mg acetomerocetol in each cubic centimeter.

U. S. patent 2,415,754

MERCOCRESOLS.—*Mercresin* (Уржон).—A mixture consisting of equal parts by weight of *sec.*-amyltricresol and *o*-hydroxyphenylmercuric chloride. Mercocresols is used in the form of a tincture containing 0.1 per cent secondary amyltricresol and 0.1 per cent *o*-hydroxyphenylmercuric chloride dissolved in a solution containing 10 per cent acetone, 50 per cent alcohol, and water. The structural formula of mercocresols may be represented as follows:



Actions and Uses.—Mercocresols, the combination of cresol derivatives and an organic mercury compound, possesses germicidal, fungicidal and bacteriostatic properties peculiar to its two active parts. The actions of the two constituents supplement each other so that the mixture is approximately twice as germicidal for *Staphylococcus aureus* as the component cresol derivatives alone, and seven to ten times as germicidal as the mercury compound alone. The estimated total effect is not of that order for all patho-
 summation
 components.
 the short-
 antiseptics,

as applied externally
 as
 act
 to
 mucous membranes and for irrigation of certain body cavities and deep infected wounds.

The toxicity of mercocresols is principally that of the organic mercurial component.

Dosage.—Mercocresols is applied topically in the undiluted tinc-

ture (containing secondary amyltricresol 1:1,000 and *o*-hydroxyphenylmercuric chloride 1:1,000) to all superficial wounds and for surgical preparation of the intact skin. It may be applied similarly to the ear, nose and throat, but dilutions of 1:5 to 1:20 should be used for irrigation or wet dressings applied to these areas.

mended, for irrigation, instillation or lavage of the bladder and urethra dilutions of 1:10 to 1:20 should be used. Dilutions of 1:10 to 1:20 are also employed for instillation in the eye.

Mercocresols is compatible with both acids and alkalis and does not precipitate with the chlorides of the body fluids.

THE UPJOHN COMPANY

Tincture Mercresin: 60 (Pistol Grip), 118 and 473 cc. and 3 785 liter bottles. A tinted solution of 0.2 per cent mercocresols, in a mixture of 10 per cent acetone, 50 per cent alcohol and water.

Tincture Mercresin (Stainless): 118 and 473 cc. and 3 785 liter bottles. An untinted solution of 0.2 per cent mercocresols in a mixture of 10 per cent acetone, 50 per cent alcohol and water.

PHENYLMERCURIC NITRATE-N.F.—Merphenyl Nitrate (Basic) (HAMILTON)—"Phenylmercuric Nitrate is a mixture of phenyl-

Actions and Uses—Solution or ointment of phenylmercuric nitrate is used externally as an antiseptic for the prophylactic and therapeutic disinfection of the skin, superficial abrasions, lacerations, wounds and infections.

Dosage.—For prophylactic disinfection of the intact skin and

parts of water). When used as a wet dressing, the 1:24,000 dilution should be prevented from becoming too concentrated, as the result of unavoidable evaporation, by the addition of 0.5 per cent of sodium chloride. To each 500 cc. of diluted solution, 2.5 Gm. of noniodized table salt may be added. This does not produce excessive precipitation. The full strength (1:1,500) solution never should be used to wet bandages or dressings. The 1:1,500 oxycholesterin base ointment also may be employed for the prophylactic disinfection of minor injuries or may be applied twice daily for the treatment of superficial infections.

HAMILTON LABORATORIES, INC.

Ointment Merphenyl Nitrate (*Basic*) 1:1,500: 28.3 Gm. tubes. A water-in-oil emulsion ($\frac{2}{3}$ aqueous, $\frac{1}{3}$ oil phase) of an oxycholesterin base containing 0.067 per cent basic phenylmercuric nitrate with 0.1 per cent boric acid.

Solution Merphenyl Nitrate (*Basic*) 1:1,500: 473 cc. and 3.78 liter bottles. An aqueous solution containing 0.067 per cent basic phenylmercuric nitrate with 0.1 per cent boric acid.

U. S. trademark 318,039.

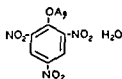
Silver

Silver compounds are used in medicine to secure caustic, astringent and antiseptic effects. These results are produced by the free silver ions. When caustic effects are desired, silver nitrate is preferred, because the colloidal compounds of silver are not caustic. As an astringent, also, silver nitrate is the compound of choice, but it must be used in weaker solutions; silver picrate acts similarly. The antiseptic action of silver nitrate is complicated by irritation, pain, astringency and corrosion. These may be desirable for the destruction of tissue or the stimulation of indolent wounds; but when they are not necessary, these actions may be avoided by the use of colloidal silver preparations.

The routine instillation of a few drops of 1 per cent solution of silver nitrate into infants' eyes immediately after birth for the prophylaxis of ophthalmia neonatorum is practiced widely and is required by law in many states.

Caution.—The long continued use of any silver preparation may produce irremediable discoloration of the skin or mucous membrane (argyria).

SILVER PICRATE.—Picragol (WYETH).—Silver trinitrophenolate monohydrate.—The structural formula of silver picrate may be represented as follows.



Physical Properties.—Silver picrate forms yellow crystals, which slowly discolor in sunlight. It is sparingly soluble in alcohol and water, slightly soluble in acetone and glycerin and very slightly soluble in chloroform and ether.

Actions and Uses.—Silver picrate is used in the treatment of vaginitis due to *Trichomonas vaginalis* and *Monilia albicans* in the form of a compound powder for insufflation and suppositories for insertion. Protracted use of this compound may give rise to argyria, because of its silver content, and nephritis, because of its picric acid content. Therefore, it is necessary to watch the skin

for signs of argyria, and the urine for albumin and casts. In all vaginal insufflation in the pregnant female, the physician should exercise every precaution to prevent positive pressure in the vagina because of danger of breaking the enlarged veins and introducing air into the vena circulation.

Dosage.—Concentrations of 1 to 2 per cent are used in the form of compound powder and vaginal suppositories.

The compound powder is administered by means of an insufflator or other surgical "powder blower." The vaginal suppository containing 0.13 Gm. in a boroglyceride gelatin base is intended primarily to be used as an adjunct in the treatment of this condition.

WYETH LABORATORIES, INC.

Powder Picragol Compound 1%: 5 Gm. bottles 1 per cent silver picrate in purified kaolin.

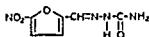
Vaginal Suppositories Picragol. 0.13 Gm silver picrate in a boroglyceride gelatin base.

U. S. trademark 421,338

Nitrofuran Derivatives

The nitrofurans are substitution products of furan in which the 5-nitro group is essential for their antimicrobial activity. Depending largely on their concentration, they are bacteriostatic or bactericidal, probably through inhibition of enzymatic oxidative processes. Their bacteriostatic activity apparently results from a reversible inhibition of enzymes concerned with the dissimilation of pyruvate. The mechanism of the bactericidal action is unknown. In vitro, it is fairly difficult to develop bacterial strains that are resistant to nitrofurans. When such resistance occurs, it is of a relatively low degree. Cross resistance has been observed to some other 5-nitro-2-furaldehyde derivatives but not to chloramphenicol. Induced bacterial resistance to sulfathiazole, penicillin, chlortetracycline or streptomycin does not appear to entail resistance to the nitrofurans. Prolonged exposure to these compounds may produce sensitization in some patients.

The structural formula of nitrofurazone may be represented as follows:



Physical Properties.—Nitrofurazone is an odorless, lemon-yellow, crystalline powder, which turns brownish black on heating and decomposes between 236 and 240°. It is nearly tasteless but de-

velops a bitter aftertaste. One part of nitrofurazone is soluble in 590 parts of alcohol, 350 parts of propylene glycol and 4200 parts of water. It is slightly soluble in polyethylene glycol mixtures and is practically insoluble in ether. The crystals darken on prolonged exposure to light.

Actions and Uses.—Nitrofurazone is a substituted furan compound possessing bacteriostatic and bactericidal properties; it is inhibitory in broth in concentrations of 1:100,000 to 1:200,000 and bactericidal at 1:50,000 to 1:75,000. It is effective in vitro and in

taminated wounds, burns, ulcerations and pyodermas, especially impetigo and ecthyma. It is also useful topically as an adjunct in the management of acute or chronic purulent otitis of bacterial origin arising from either the external or the middle ear, except in severe otitis media associated with cholesteatoma. It may be useful as an adjunct to surgery in the preparation of areas for skin grafting and in the treatment of osteomyelitis. Daily application for periods of 10 days or longer may produce a local reaction in some cases. Intolerance to local use of nitrofurazone has been observed and may be an indication for withdrawing the drug. Continuous applications for 5 days may produce sensitization and generalized allergic skin reaction. Photosensitization from sunlight has not been encountered.

It is useful for ophthalmic application in the management of bacterial eye infections, including treatment of purulent conjunctivitis and prophylaxis or treatment against infections in corneal abrasions and ulcers and following chalazion operations and the removal of embedded foreign bodies from the cornea. Local sensi-

likely.

base

or solution containing a concentration of 1:500 (0.2 per cent). It is applied locally either directly or to dressings that are then used to cover the infected area. The base is water soluble, softens at body temperature and, thus, may require special coverings to maintain effective contact with certain areas. Contact of the ointment with the infecting micro-organisms is essential for their destruction. Dressings may be reinforced with cellophane or similar material, and petrolatum gauze may be used for a barrier to limit absorption into the dressing. On exposure to light, the bright yellow nitrofurazone turns dark brown. This is not associated with any ill effects and may be avoided by covering it with light dressings.

For topical application in the control of purulent otitis, 0.5 cc of a 0.2 per cent solution is instilled into the external meatus three or four times daily. The application should be preceded with cleansing of the meatus by irrigation and drying. A cotton plug

may be repeated after each application to retain the solution, or it

3 in the eye
times daily,

and as a 1 per cent ointment, especially for supplemental night time use. The ointment usually is contraindicated in cases of perforated injuries of the eyeball

EATON LABORATORIES

Ear Solution Furacin 0.2%: 15 cc dropper bottles. An anhydrous solution in polyethylene glycol 300

Ophthalmic Ointment Furacin 1%: 3.54 Gm tubes. An ointment containing 10 mg of nitrofurazone in each gram

Ophthalmic Solution Furacin: 15 cc dropper bottles. An isotonic solution containing 0.2 mg of nitrofurazone in each cubic centimeter. Preserved with 0.02 per cent phenylmercuric acetate

Soluble Dressing Furacin 0.2%: 56.7 Gm. tubes; 113 Gm., 454 Gm. and 2.26 Kg. jars. An ointment containing 2 mg of nitrofurazone, 0.45 Gm. of polyethylene glycol 1540, 0.05 Gm of polyethylene glycol 4000 and 0.5 Gm of polyethylene glycol 300 in each gram.

Solution Furacin 0.2%: 118 and 473 cc bottles. A solution containing 2 mg. of nitrofurazone, 3 mg of polyethylene glycol of monoisooctyl phenyl ether in a mixture of 0.32 Gm of polyethylene glycol 300, 0.32 Gm of polyethylene glycol 1540 and water in each cubic centimeter.

U. S. patents 2,319,481 and 2,416,234. U. S. trademarks 403,279 and 441,715

Peroxides

The peroxides belong to a class of oxidizing agents (others: chlorine, ozone, perborates, permanganates) that are deleterious to bacteria by virtue of the nascent oxygen they liberate. Nascent oxygen combines rapidly with all organic matter and once combined is inert; these properties reflect the strength and weakness of these agents as germicides. All of these agents are inactivated rapidly by catalase, a ferment found in most cells. Molecular oxygen is most harmful to obligate anaerobes that produce hydrogen peroxide but do not produce catalase with which to destroy it.

Hydrogen peroxide, H_2O_2 , decomposes to water and 1 atom of nascent oxygen. Solutions of hydrogen peroxide have high surface tensions and, therefore, do not penetrate well. Because of their rapid inactivation by protein, they must be used over a long period of time. The 3 per cent commercial solutions are employed as local anti-infectives; the strong (30 per cent) solution is extremely caustic.

The liberated oxygen from hydrogen peroxide decomposition

sometimes causes effervescence. For this reason it should not be injected into closed body cavities or into abscesses from which the gas cannot escape

Hydrogen peroxide is valuable for the removal of dead organic matter from areas from which mechanical removal is difficult. Its action on bacteria increases with increased temperature and in the presence of certain salts that catalyze the release of nascent oxy-

spores.

In metallic peroxides the hydrogen of hydrogen peroxide has been replaced by metals, which slowly liberate oxygen for 24 to 48 hours. They differ in action in accordance with their solubility and the alkalinity produced by interaction of the peroxide with water. The action of peroxides also is affected by the nature of the metal that goes into solution when the peroxide is decomposed. Thus, the use of sodium peroxide is limited because a strong base is formed when it dissolves in water.

Zinc peroxide is used postoperatively to control infection although it is not effective against all micro-organisms, and the consistency of the preparations precludes deep infiltration. Disintegration of zinc peroxide leaves deposits of zinc oxide and hydroxide in the wound and increases exudation. Untoward drying of the medicament may be prevented by properly covering the area with petrolatum or zinc oxide ointment gauze.

ZINC PEROXIDE, MEDICINAL-U.S.P.—"Medicinal Zinc Peroxide consists of a mixture of zinc peroxide, zinc carbonate and zinc hydroxide. Each Gm. of Medicinal Zinc Peroxide, previously heated at 135° to 140° for 4 hours, evolves not less than 2.16 ml. of oxygen in 20 hours and not less than 0.24 ml. of oxygen in the following 4 hours" *U.S.P.*

Physical Properties.—Medicinal zinc peroxide occurs as a fine, white or faintly yellow, odorless powder. It is almost insoluble in water and organic solvents but dissolves readily in dilute acids.

Actions and Uses.—See the general statement on peroxides.

Dosage.—Zinc peroxide medicinal (powder) sterilized in small quantities (10 to 50 Gm.) by heating in a dry oven for 4 hours at exactly 140° is made up with sterile distilled water to a smooth, cream. If the cream does not come

The dose depends entirely on the size of the wound to be treated. Enough of the creamy suspension should be used to provide the

Dressings usually are changed in 24 hours but may be left for several days.

MALLINCKRODT CHEMICAL WORKS

Powder Zinc Peroxide Medicinal: 28.3, 113.4 and 454 Gm. bottles

Phenol Derivatives

Phenol derivatives include the cresols and the diphenols. Cresols are phenols in which one of the hydrogen atoms has been replaced by a methyl group. The official cresol is a mixture of the three isomers, *ortho*-, *meta*- and *para*-cresol. They are only moderately soluble in water, about 1:50, but are emulsified readily in the presence of soap and alkalis, however, excess soap and alkali diminish their germicidal efficiency.

The antibacterial specificities of the cresols closely parallel those of phenol. Cresols are highly effective against acid-fast bacteria but have limited virucidal value, they are not sporicidal. In contrast to other disinfectants, the cresol compounds retain their germicidal properties remarkably well in the presence of organic matter.

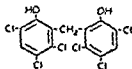
The toxicity and local actions of the cresols, as of other phenols, may be diminished by "masking" the active OH group by the formation of esters.

Diphenols, such as hexachlorophene, are derivatives of diphenyl, diphenylmethane and diphenylsulfide. These substances are weakly acidic, and it is believed that when combined with excess alkali, as in soap, only one of the two phenolic groups is neutralized, while the other retains antibacterial properties.

HEXACHLOROPHENE—U.S.P.—*Gamphen* (ETHICON)—*Hex-O-San* (RETOY)—
(CENTRAL)—2,2'-chlorophene, dried

98 per cent of $C_{12}H_6Cl_6O_2$

The structural formula of hexachlorophene may be represented as follows



Physical Properties—Hexachlorophene is an odorless (or with a

detergent creams, oils and other vehicles for topical application to reduce the numbers and to inhibit the metabolism of micro-

organisms that occur naturally and pathogenically in the skin bacterial flora.

Residual amounts of hexachlorophene, which are adsorbed on the skin, maintain a reduction in numbers of bacteria. Optimum results are obtained only with regular daily application of the agent to the skin surface; substitution of other cleansing agents, including water, removes the adsorbed hexachlorophene with a resultant rapid increase in numbers and metabolism of micro-organisms. Application of alcohol or other organic solvents to the skin should be avoided. The activity of hexachlorophene, like that of many antibacterial agents, is considerably reduced by blood serum and other organic matter.

Hexachlorophene is effective against gram-positive bacteria; the gram-negative organisms are much more resistant to its action. No evidence presently is available concerning its efficacy against acid-fast bacteria, fungi, bacterial spores or viruses. Irritant and toxic effects of hexachlorophene on the skin surface, even after long-continued daily use, have been reported infrequently. Data have not been presented on the possibility of acquired resistance of the skin bacterial flora following prolonged use of hexachlorophene.

Products containing hexachlorophene are used for preoperative scrubbing and preoperative and postoperative preparation of patients' skin. When used continually, hexachlorophene is also an effective prophylactic agent in decreasing the incidence and severity

chemical agent should be relied on as a substitute for mechanical cleansing of the skin.

Dosage.—For use as an antibacterial agent hexachlorophene may be incorporated in a number of vehicles, i.e., soap, detergents, creams and oils. Concentrations of 2 to 3 per cent in bar and liquid soaps (based on the amount of anhydrous soap present) and in detergent preparations, and concentrations of 0.5 to 1 per cent in products that are applied to the skin undiluted are efficacious in reducing the number of micro-organisms inherent in the skin bacterial flora; maintenance of reduced numbers depends upon regular daily applications of the agent to the treated area. Concentrations in excess of 3 per cent have not yet been shown to be more effective.

CENTRAL CHEMICAL COMPANY, INC.

Liquid Soap Surgi-Cen: 3.75, 18.9, 56.7, 113.4, 132.4 and 208.1 liter containers. A soap containing 1 per cent hexachlorophene (2.75 per cent anhydrous soap basis).

U. S. trademark 582,456

ETHICON SUTURE LABORATORIES, INC.

Surgical Soap Gamphen: 56.7 and 127.5 Gm. cakes. A soap containing 2 per cent hexachlorophene.

U. S. trademark 532,820

J. I. HOLCOMB MANUFACTURING COMPANY

Liquid Soap Hexachlorophene: 3.78, 18.9, 56.7, 113.4 and 208.1 liter containers. A soap containing 0.5 per cent hexachlorophene (2 per cent anhydrous soap basis).

HUNTINGTON LABORATORIES, INC.

Germa-Medica Liquid Surgical Soap Hexachlorophene: 3.78 and 18.9 liter cans; 56.7, 75.6, 113.5, 132.4, 208.1 and 245.9 liter drums A liquid soap containing 1 per cent hexachlorophene (2.5 per cent anhydrous soap basis).

U S trademark 213,093

REYORT PHARMACEUTICAL COMPANY, INC.

Surgical Soap Hex-O-San: 3.78 and 18.9 liter cans and 56.7, 113.5 and 208.1 liter drums A soap containing 0.72 per cent hexachlorophene (2 per cent anhydrous soap basis)

VESTAL, INC

Septisol with Hexachlorophene 0.75%: 3.78 liter pails and 113.5 and 208.1 liter drums A soap containing 0.75 per cent hexachlorophene (2 per cent anhydrous soap basis)

U S trademark 245,239

WINTROP-STEARN, INC.

phisoHex: 473 cc and 3.78 liter bottles and 148 cc. squeeze bottles. A detergent lotion containing 3 per cent of hexachlorophene (18.4 per cent anhydrous detergent basis)

U S patent 2,303,932 U S trademark 408,558.

Surface-Active Compounds

Interference with the physicochemical properties of micro-organisms and resultant changes in bacterial metabolism are effected by antiseptics and disinfectants. Certain of these substances have the property of altering surfaces and interfaces, chemical agents that act as local anti-infectives and possess this property are referred to as "detergents." They are subclassified as anionic, cationic and nonionic on the basis of the varying activity encountered in salts that have one ion of much greater molecular weight than the other, on the postulation that un-ionized complexes are formed between chemical agents and micro-organisms.

None of these compounds possesses virucidal, sporicidal or fungicidal properties, nor are they effective against acid-fast bacteria. Attempts have been made to correlate the ability of these compounds to reduce surface tension with their anti-infective action. That this factor alone is not responsible for their antibacterial action is apparent from the fact that many substances which are good surface-tension depressors are poor anti-infectives. Also, at the concentrations at which the surface-active agents act as anti-infectives, the surface tension does not differ appreciably from that of a good culture medium. Certain types of surface-tension depressors

have been employed in culture media to enhance and accelerate the growth of acid-fast micro-organisms.

The antibacterial action of all surface-active agents is reduced greatly in the presence of organic matter (i.e., blood serum, pus, etc.) In vitro methods that do not utilize organic matter in the antibacterial evaluation of surface-active agents are of little value and cannot be interpreted as conditions of actual use.

Anionic Agents

These agents are the neutral or faintly alkaline sodium (etc.) salts of acids of high molecular weight, exemplified by common soaps, ammonium and calcium mandelates, alkyl sulfates, salts of bile acids and a class of neutral, colored substances known as "acid dyes" (e.g., acid fuchsin).

These agents are effective only on substances at pH values more acid than that of blood, they have been found useless in infected wounds, moderately useful in skin disinfection and very effective in the disinfection of the urinary tract, provided sufficient acidity is maintained and the substances (i.e., mandelates) are excreted unchanged.

The anionic agents, in general, are most effective against the gram-positive organisms.

Theories concerning their mode of action on the bacterial cell include (1) possible interaction of their acidic ions with the basic groups (i.e., enzyme systems) of the cell to form feebly ionized compounds and (2) interpretation of increased action in an acid medium to mean that the undissociated acid is more "active" than the ion. The latter theory would lose ground if it were found that increasing the acidic nature of the anions raised their antibacterial action.

Anionic compounds inactivate cationic agents.

MANDELIC ACID DERIVATIVES.—See the chapter on systemic anti-infectives.

SODIUM TETRADECYL SULFATE.—For monograph see the chapter on sclerosing agents.

Cationic Agents

The neutral salts (hydrochlorides, etc.) of bases of high molecular weight comprise this group. They include fatty amine salts, quaternary ammonium compounds or alkyl pyridinium compounds and the so-called basic dyes, such as the polyphenylmethane antiseptics (brilliant green, auramine and crystal violet) and the acridine antiseptics (proflavine and acriflavine hydrochloride). The dyes are discussed in another section of this chapter.

Cationic surface-active agents bear positive electrical charges on their hydrophobic groups. Cationic agents are effective against both gram-positive and gram-negative organisms but higher concentrations are required to kill the latter type. The antibacterial action

of these agents increases as the pH is increased. Cationic agents possess a low order of toxicity although some of the fatty salts appear to be primary irritants or skin sensitizers.

Since the antibacterial action of cationic compounds is opposed by that of anionic agents (soap in concentrations as low as 0.1 per cent decreases the action), their application to the intact skin to be prepared for surgery must be preceded by thorough rinsing of the soap-cleaned areas, first with water and then with 70 per cent alcohol. The use of alcohol diminishes the ionization of ordinary soap solution, so that the inactivating chemical union of soap with the disinfectant is prevented.

Cationic detergents are not virucidal, sporicidal or fungicidal and cannot be relied upon for sterilization of surgical instruments and heat-labile articles. However, they may be used to preserve the sterility of articles during storage.

The "quaternary ammonium compounds" are synthetic salts of organic, nitrogen-containing compounds. The properties of the two types are similar: (1) The four hydrogens of the ammonium radical, $[NH_4]^+$, are replaced by alkyl or aryl groups and (2) the nitrogen of heterocyclic radicals is alkylated or arylated completely.

The antibacterial properties of these compounds are due to their chemical reactivity and to their adsorbability, the same properties often account for their failure as germicides. They are adsorbed completely by charcoal and to a lesser degree by agar. Due to this high degree of adsorption on the bacterial wall, test methods that incorporate a neutralizing or desorbing substance are employed for determining the antibacterial action of these compounds. Methods which do not include this procedure measure only bacteriostatic properties of the agent. Quaternary ammonium compounds combine readily with proteins and, therefore, are less efficient in the presence of serum and other organic matter. Some phosphates diminish their effectiveness, fats affect them physically. The many quaternary ammonium compounds that have been synthesized vary in their antibacterial action, some are inefficient as disinfectants and sanitizers.

The logarithmic survival curve of bacteria subjected to the action of quaternary ammonium compounds is straight only for the killing of the first 99.9 per cent, after that, the death rate decreases and the last survivors display marked resistance.

Certain limitations are emphasized when the quaternary ammonium compounds are utilized as skin disinfectants because they form a film on the skin under which bacteria remain viable. The film is moderately resistant to mechanical trauma, its inner surface possesses little antibacterial action, whereas the outer surface exerts considerable action. Disinfection of the surgeon's hands in gloveless surgery depends upon the mechanical stability of the film and upon the neutralizing effect of tissue fluids and blood. Sterilization of the operative field and the incision itself by these agents is doubtful.

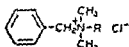
The quaternaries have been recommended as satisfactory sanitizing rinses for reduction of the bacterial flora on eating and drinking utensils and dairy equipment, provided thorough me-

chanical cleansing and removal of anionic detergents precedes the rinse. Rise in temperature increases the efficiency of these and other disinfectants

Strains of *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis* are particularly resistant to these agents. Bacterial spores remain viable even after prolonged contact with solutions of the quaternaries. Utility of these agents for combating bacterial and fungal infections is not established

In the concentrations commonly employed the quaternary ammonium salts are not toxic to animals.

BENZALKONIUM CHLORIDE-U.S.P.—Zephiran Chloride (WINTHROP-STEARNs)—Alkylbenzyltrimethylammonium chloride.—“Benzalkonium Chloride is a mixture of alkylbenzyltrimethylammonium chlorides of the general formula, $[C_6H_5CH_2N(CH_3)_2R]^+Cl^-$, in which R represents a mixture of the alkyls from C_8H_{17} to $C_{18}H_{37}$. It contains, when calculated to the anhydrous basis, not less than 97 per cent and not more than 103 per cent of $[C_6H_5CH_2N(CH_3)_2R]^+Cl^-$ ” U.S.P. The structural formula of benzalkonium chloride may be represented as follows:



Physical Properties.—Benzalkonium chloride occurs as a white or yellowish white, amorphous powder or in the form of gelatinous pieces. It has an aromatic odor and a very bitter taste. Its solution is slightly alkaline to litmus paper and foams strongly when shaken. It is very soluble in water, in alcohol or in acetone, it is almost insoluble in ether and is slightly soluble in benzene.

Actions and Uses.—Benzalkonium chloride properly diluted is an effective, noninjurious, surface disinfectant which is germicidal for many pathogenic nonsporulating bacteria and fungi after several minutes' exposure. Solutions of benzalkonium chloride have low surface tension and possess detergent, keratolytic and emulsifying actions, properties that assist penetration and wetting of tissue surfaces. Organic matter and anionic compounds rapidly reduce its activity.

Effective concentrations of benzalkonium chloride are emollient and of comparatively low toxicity. Rabbits tolerate from 3 to 5 cc. of a 1 per cent aqueous solution orally or 1.2 cc. per kilogram of body weight, administered subcutaneously or intraperitoneally. Application of various concentrations to the skin of these animals, shows that a 0.1 per cent solution is the highest concentration that may be allowed to remain in contact for 24 hours without producing irritation.

Benzalkonium chloride is suitable for general use in the prophylactic disinfection of the intact skin and mucous membranes and in the treatment of superficial injuries and infected wounds. It is used also to preserve the sterility of surgical instruments and rubber

actions and Uses.—Cetyl pyridinium chloride, a quaternary ammonium salt, is a cationic detergent that possesses useful surface-active as well as antiseptic properties against sensitive nonsporulating bacteria. It is employed in aqueous solution or tincture in appropriate dilutions for topical application in the preoperative disinfection of the intact skin and the prophylactic antiseptics of superficial minor wounds. It is used also by topical application or irrigation for therapeutic disinfection of accessible mucous membranes.

Cetyl pyridinium chloride is subject to the shortcomings of other cationic detergents employed as germicides in that its action is opposed by anionic detergents such as ordinary soap, may be reduced in the presence of serum and tissue fluids and is not reliable against clostridial spores.

Dosage.—Intact skin may be prepared for surgery by scrubbing for 5 to 10 minutes with an aqueous solution of cetyl pyridinium chloride 1:100. When the conventional soap-alcohol-ether-germicide method is to be employed, 1:500 or 1:1,000 tincture dilutions may be used as the germicide if soap is completely removed before application. Similar dilutions of the tincture or a 1:1,000 aqueous solution may be used for topical application to minor lacerations and abrasions. For disinfection of delicate mucous membranes or extensive areas of exposed tissue, 1:5,000 to 1:10,000 solutions should be used.

THE W. S. MERRELL COMPANY

Concentrated Solution Ceepryn Chloride 15%: 130 cc. and 3.72 liter bottles. An aqueous solution containing 0.1 Gm. of cetyl pyridinium chloride and 10 mg. of monobasic sodium phosphate in each cubic centimeter for the preparation of solutions and tinctures for external use.

Isotonic Solution Ceepryn Chloride 1:1,000: 450 cc. and 3.72 liter bottles. A solution containing 1 mg. of cetyl pyridinium chloride in each cubic centimeter which is made isotonic by addition of monobasic sodium phosphate and disodium phosphate.

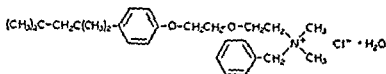
Tincture Ceepryn Chloride 1:200 (Tinted): 450 cc. and 3.72 liter bottles. An alcohol-acetone-aqueous solution containing 5 mg. of cetyl pyridinium chloride in each cubic centimeter.

Tincture Ceepryn Chloride 1:500 (Tinted): 450 cc. and 3.72 liter bottles. An alcohol-acetone-aqueous solution containing 2 mg. of cetyl pyridinium chloride in each cubic centimeter.

U. S. patent 2,295,504 U. S. trademark 328,183.

METHYLBENZETHONIUM CHLORIDE.—*Diaperene Chloride* (HOMEMAKERS' PRODUCTS).—Benzyl(dimethyl[2-[2-(p-t,3,3-tetramethylbutylcresoxy)ethoxy]ethyl]ammonium chloride. — The structural formula of methylbenzethonium chloride may be represented as follows.

The structural formula of benzethonium chloride may be represented as follows.



Physical Properties.—Benzethonium chloride forms colorless, odorless crystals that are very bitter. It may be recrystallized from chloroform, by the addition of ether, in the form of very thin plates, which may be hexagonal. Mineral acids and many salt solutions precipitate benzethonium chloride from solutions more concentrated than 2 per cent, as an oil which crystallizes on drying and has the same properties as benzethonium chloride. A solution of benzethonium chloride yields a flocculent white precipitate with soap solutions. The pH of a 1 per cent solution of benzethonium chloride is between 4.8 and 5.5.

Actions and Uses.—Benzethonium chloride is a synthetic quaternary ammonium compound belonging to the cationic group of detergents. It inhibits metabolism and viability of commonly occurring nonsporulating bacteria. Both tinctures and aqueous solutions are used as general germicides and antiseptics. Soap and other anionic detergents, as well as organic matter, are incompatible with this agent.

Dosage.—Tincture benzethonium chloride 1:500 and aqueous solution benzethonium chloride 1:1,000 are used undiluted. For use in the nose and eye only the solution should be used, diluted with four parts of water.

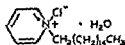
PARKE, DAVIS & COMPANY

Solution Phemerol Chloride 1:1,000: 480 cc and 3.84 liter bottles.

Tincture Phemerol Chloride 1:500: 480 cc and 3.84 liter bottles.

U S patent 2,115,350 U S trademark 305,545

CETYL PYRIDINIUM CHLORIDE—Cespryn Chloride (MERRELL).—The monohydrate of the quaternary salt of pyridine and cetyl chloride. The structural formula of cetyl pyridinium chloride may be represented as follows.



Physical Properties.—Cetyl pyridinium chloride is a white powder with a slight odor. It melts between 77 and 83°. It is very soluble in alcohol, chloroform and water and only very slightly soluble in benzene and ether. The pH of a 1 per cent solution is 6.0 to 7.0, as determined by the use of indicators (instruments with glass electrodes give variable results).

Actions and Uses.—Cetyl pyridinium chloride, a quaternary ammonium salt, is a cationic detergent that possesses useful surface-active as well as antiseptic properties against sensitive nonsporulating bacteria. It is employed in aqueous solution or tincture in

Dosage.—Intact skin may be prepared for surgery by scrubbing for 5 to 10 minutes with an aqueous solution of cetyl pyridinium chloride 1:100. When the conventional soap-alcohol-ether-germicide method is to be employed, 1:500 or 1:1,000 tincture dilutions may be used as the germicide if soap is completely removed before application. Similar dilutions of the tincture or a 1:1,000 aqueous solution may be used for topical application to minor lacerations and abrasions. For disinfection of delicate mucous membranes or extensive areas of exposed tissue, 1:5,000 to 1:10,000 solutions should be used.

THE W. S. MERRELL COMPANY

Concentrated Solution Ceopryn Chloride 10%: 180 cc. and 3.78 liter bottles. An aqueous solution containing 0.1 Gm. of cetyl pyridinium chloride and 80 mg. of monobasic sodium phosphate in each cubic centimeter for the preparation of solutions and tinctures for external use.

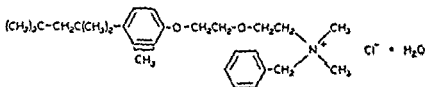
Isotonic Solution Ceopryn Chloride 1:1,000: 480 cc. and 3.78 liter bottles. A solution containing 1 mg. of cetyl pyridinium chloride in each cubic centimeter which is made isotonic by addition of monobasic sodium phosphate and disodium phosphate.

Tincture Ceopryn Chloride 1:200 (Tinted): 480 cc. and 3.78 liter bottles. An alcohol-acetone-aqueous solution containing 5 mg. of cetyl pyridinium chloride in each cubic centimeter.

Tincture Ceopryn Chloride 1:500 (Tinted): 480 cc. and 3.78 liter bottles. An alcohol-acetone aqueous solution containing 2 mg. of cetyl pyridinium chloride in each cubic centimeter.

U. S. patent 2,293,504 U. S. trademark 398,185.

METHYLBENZETHONIUM CHLORIDE. — Dispersene Chloride (HOMEMAKERS' PRODUCTS) — Benzyl dimethyl[2-{2-(p-1,1,3,3-tetramethylbutyl)crotyloxy}ethoxyethyl]ammonium chloride — The structural formula of methylbenzethonium chloride may be represented as follows:



Physical Properties.—Methylbenzethonium chloride forms colorless, odorless crystals with a bitter taste. It melts between 161 and 163° on a hot-stage microscope. It is readily soluble in alcohol, hot benzene, Cellosolve, chloroform and water. It is insoluble in carbon tetrachloride and ether.

Actions and Uses.—Methylbenzethonium chloride is a quaternary ammonium salt with surface-active and disinfectant properties similar to those of other cationic detergents. Its use is recognized only for bacteriostasis of urea-splitting organisms that may be involved in diaper dermatitis. Its employment, therefore, is restricted to the prevention of ammonia dermatitis in infants by disinfection of diapers. Its action against other bacteria has not been studied sufficiently to warrant its use as a general purpose local antiseptic. When other forms of rash appear or actual treatment becomes necessary, the supervision of a physician is required. The systemic toxicity and local sensitizing properties of methylbenzethonium chloride are sufficiently low to permit its safe use in the home for the disinfection of infant diapers.

Dosage.—Methylbenzethonium chloride is used in a clear solution of approximately 1:25,000. The quantity of solution made by the addition of 0.09 Gm. (one tablet crushed to powder) to about 2,000 cc. (2 quarts) of warm water is sufficient for rinsing six diapers. The washed diapers should be freed of soap before rinsing, to avoid soap inhibition of the disinfectant, and placed in an empty basin. The solution then is poured over each diaper, thoroughly stirred and allowed to stand for at least 3 minutes. Diapers then are wrung out and dried without rerinsing. This procedure usually will protect the diapers against urine decomposition for 15 hours of use, but it is not recommended that wet diapers be left unchanged, since this may encourage maceration of the skin or chilling of the infant. Rinsing of the night diapers usually provides sufficient protection, but when necessary the daytime diapers also should be rinsed.

Precautions should be taken to avoid accidental oral ingestion of the tablets.

CREMO PURO MANUFACTURING CORPORATION

Powder Methylbenzethonium Chloride: Bulk; for manufacturing use.

HOMEMAKERS' PRODUCTS CORPORATION

Tablets Diaparene Chloride: 0.09 Gm.

U. S. patent 2,643,969. U. S. trademark 529,343.

ANTIFUNGAL AGENTS

The superficial fungus infections are amenable to topical medication. Two members, *propionic* and *caprylic*, of the series of saturated fatty acids of the general formula $C_nH_{2n}O_2$ and one member, *undecylenic*, of the series of unsaturated fatty acids of the general formula $C_nH_{2n-2}O_2$ are employed as antifungal agents although their fungistatic action *in vitro* is weak. Either the acids or their salts are used. Certain derivatives of petroleum hydrocarbons and salicylic acid and its salts likewise have been used for their antifungal action. Any effectiveness of salicylic acid probably is due to its keratolytic action rather than to a direct action on fungi. All of the above types of compounds usually are applied in the form of ointments, frequently in the form of powders and occasionally as solutions. The dyes practically always are employed as solution.

The dyes are used in medicine for other than their antifungal action. They are employed as chemotherapeutic agents and for special effects upon tissue cells. The local antiseptic action of dyes results from their bacteriostatic and bactericidal powers. These are often specific.

The dyes used in medicine are nearly all organic, synthetic products. They may be roughly divided into six classes: (1) the azo dyes, (2) the acridine dyes, such as acriflavine hydrochloride, acriflavine base and proflavine, (3) the fluorescein dyes, either as fluorescein or combined with the metal mercury, such as mercurochrome soluble and flumerin; (4) the phenolphthalein dyes such as phenolphthalein and phenolsulfonphthalein and their chlorine, bromine and iodine substitution products, (5) the triphenylmethane or rosaniline series, a large list of widely used substances, such as gentian violet, crystal violet, methyl violet and fuchsin; (6) miscellaneous dyes, such as methylene blue. Much confusion exists because of the varying composition of similar dyes produced by different manufacturers of commercial dyestuffs. Usually the commercial dye contains a diluent, such as dextrin or salts, and is judged by tinctorial power. In order to obtain comparable results in the clinic, the dyes should be of constant composition, preferably without diluent. Strict attention should be paid to the actual dye content of each lot of dye.

The triphenylmethane (rosaniline) dyes used medicinally are typified by such substances as fuchsin, crystal violet and brilliant green.

Crystal violet has a selective action on gram-positive organisms, in fact, the action of the dye is so selective that often a "strain within a species" is not affected. The selective power of acid fuchsin (the acid sodium salt of fuchsin disulfonic and trisulfonic acids) is in some respects opposite to that of crystal violet, a culture of the gram-negative organism *Ser. marcescens* (*Prodigiosus*) being killed by the acid fuchsin, while the gram-positive *B. anthracis* is unaffected, at a temperature of about 50°. Acid fuchsin is incompatible with crystal violet. None of the rosaniline dyes is a strong bactericide.

Rosaniline dyes are employed for the treatment of superficial fungous infections of the skin. Fuchsin, the dye component of carbol-fuchsin paint, is employed widely for this purpose, as are also gentian violet and the acridine dye, acriflavine. The principal disadvantage of these dyes is that they stain clothing.

CAPRYLIC COMPOUND.—*Naprylate* (STRASENBURG).—A mixture of 10 per cent sodium caprylate and 5 per cent zinc caprylate. Their structural formulas may be represented as follows:



Sodium caprylate

Zinc caprylate

Physical Properties.—Caprylic compound is a fine, white powder with a characteristic odor. It is partially soluble in water and is slightly soluble in alcohol.

Actions and Uses.—Caprylic compound has been found useful for the prevention and treatment of dermatophytosis pedis and for the control of other superficial fungous infections of the skin and accessible mucous membranes. Applied topically, it is effective against infection due to trichophytons, microsporons and *Monilia albicans*. Moderate concentrations of caprylic acid salts do not produce irritation or sensitization of the skin and are not subject to absorption from the skin or mucous membranes.

Dosage.—Caprylic compound powder or ointment is applied topically to the skin after the affected part has been cleaned thoroughly. The two may be used concomitantly, the powder being applied during the day and the ointment during the night. The powder may be dusted into the shoes and stockings for the control of susceptible fungous infections involving the feet. The ointment also is used in the treatment of monilial stomatitis or thrush.

For the control of monilial vulvovaginitis, caprylic compound is applied in the form of powder by insufflation and in the form of an ointment by means of a vaginal applicator. A 5 per cent solution of sodium caprylate (prepared by diluting a 20 per cent solution with 3 parts of water) may be used in stubborn cases for preliminary cleansing of the vagina prior to application of caprylic compound. Approximately 30 cc. of a 20 per cent solution of sodium caprylate may be added to 1,000 cc. of lukewarm water as a cleansing douche during therapy with caprylic compound. During pregnancy, this type of treatment should not be used after the seventh month.

R. J. STRASENBURG COMPANY

Ointment Naprylate: 21.25 Gm tubes and 454 Gm jars. An ointment containing 0.1 Gm of sodium caprylate and 50 mg. of zinc caprylate in each gram.

Powder Naprylate: 35.43 Gm. flexible plastic bottles. A powder containing 0.1 Gm. of sodium caprylate and 50 mg. of zinc caprylate in each gram.

CARBOL-FUCHSIN PAINT.—CARBOL-FUCHSIN SOLUTION.—N F.—Carfusin (RORER) —Castellani's Paint—A solution containing 1 per cent boric acid, 4.5 per cent phenol, 10 per cent resorcinol, 0.3 per cent fuchsin, 5 per cent acetone and 10 per cent alcohol in water, q s

The boric acid, phenol, resorcinol, fuchsin and acetone used in the preparation of this product meet the requirements of the *U. S. Pharmacopeia* or the *National Formulary*.

Actions and Uses.—Carbol-fuchsin paint is a stabilized preparation of the original fuchsin formula known as Castellani's paint; it is employed widely for topical application to superficial fungous infections of the skin. Its use should be restricted to subacute or chronic dermatophytoses. It is of value for epidermophytosis interdigitalis pedum ("athlete's foot"), other intertriginous lesions of fungous origin, *Tinea trichophytina* (ringworm) and *Tinea imbricata*.

Carbol-fuchsin paint has the advantage over the original and subsequent preparations in that it is stable, but it must be protected against evaporation. It shares with other triphenylmethane dyes the disadvantage that it stains clothing. It never should be applied to large areas of the body or to patients who have sensitive skin. A test application of a 1:3 dilution should be made to a single small lesion before treatment is begun with the full strength paint. The ingredients are poisonous.

Dosage.—Full strength carbol-fuchsin paint is applied directly to the surface of skin lesions. Topical application once or twice daily is indicated in subacute phases, three times daily in chronic or particularly stubborn lesions. Interim use of a foot powder and twice daily change of hosiery is recommended in the treatment of epidermophytosis pedis. In cases associated with excessive drying of the skin, application of the paint may be continued in conjunction with applications of either boric acid ointment containing 2 to 5 per cent of ammoniated mercury or an ointment of petrolatum containing 1 per cent each of sulfur and salicylic acid and 25 per cent each of zinc oxide and talc.

WILLIAM H. RORER, INC.

Carfusin 30 and 120 cc bottles. A solution containing 1 per cent boric acid, 4.5 per cent phenol, 10 per cent resorcinol, 0.3 per cent fuchsin, 5 per cent acetone and 10 per cent alcohol in water, q s

U. S. trademark 509,952

THE VELTEX COMPANY

Carbol-Fuchsin Paint: 30, 60, 120 and 480 cc bottles. A solution of 1 per cent boric acid, 4.5 per cent phenol, 10 per cent resorcinol, 0.3 per cent fuchsin, 5 per cent acetone and 10 per cent alcohol in water, q s

COPARAFFINATE.—Iso-Par (MEDICAL CHEM.)—A mixture of water-insoluble isoparaffinic acids partially neutralized with iso-octyl hydroxybenzylalkyl amines. The water-insoluble isoparaffinic acids are obtained by oxidation of petroleum hydro-

carbons by the passage of a current of oxygen under pressure, at an elevated temperature and in the presence of a metallic catalyst. The water-insoluble monocarboxylic and dicarboxylic acids with 6 to 16 carbon atoms are separated and purified by fractional distillation. The hydroxybenzylidialkyl amines are combined with the isoparaffinic acids directly or in a suitable solvent. The latter then is removed by distillation.

Physical Properties.—Coparaffinate is a viscous, dark brown, oily liquid with the characteristic odor of burnt petroleum. It is immiscible with water but freely miscible with alcohol and volatile and fixed oils.

Actions and Uses.—Coparaffinate ointment is for external use only. Thick or tight bandaging may cause irritation. Coparaffinate is of value in the treatment of pruritus ani and vaginae, mycotic infections of the hands and feet, eczemas of the ear and certain dermatologic manifestations of allergy. This ointment is stimulating, lowers the levels of irritability of the skin and is in varying degrees bactericidal and fungicidal.

Dosage.—It should be applied with a rubber finger stall, a small wad of absorbent cotton or gauze or other convenient applicator, since it possesses an odor that may be objectionable if it persists on the fingers. The first applications may cause a temporary burning sensation. The ointment should be applied to the affected area in the evening before retiring and again in the morning, if necessary, it may be applied more frequently. The majority of cases respond within 3 to 5 days, but others may require up to 2 weeks. If relief is not obtained by that time, some other form of treatment should be substituted.

MEDICAL CHEMICALS, INC.

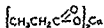
Ointment Iso-Par: 14, 78.5, 114 and 454 Gm jars. An ointment containing 17 per cent coparaffinate and 4 per cent titanium dioxide in a base consisting of beeswax, cetyl alcohol, lanolin and petrolatum.

U S patent 2,262,720. U S trademark 365,069

PROPIONATE-CAPRYLATE MIXTURES.—Preparations in which the formulation is varied with respect to both the ingredients and their concentrations according to the dosage form. The active ingredients are chosen from the following calcium propionate, caprylic acid, propionic acid, sodium propionate-N.F., zinc caprylate and zinc propionate. Their structural formulas may be represented as follows.



Caprylic acid



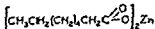
Calcium propionate



Propionic acid



Sodium propionate



Zinc caprylate



Zinc propionate

Actions and Uses.—Propionate-caprylate mixtures are used against superficial fungous infections, especially dermatophytosis of the feet, hands and groin.

Dosage.—Cleanse the affected parts and apply morning and night.

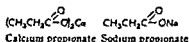
WYETH LABORATORIES, INC.

Ointment Sopronol Propionate-Caprylates Compound: 30 and 120 Gm. tubes. A water-soluble ointment containing 12.3 per cent sodium propionate, 2.7 per cent propionic acid, 10 per cent sodium caprylate, 5 per cent zinc caprylate and 0.1 per cent dioctyl sodium sulfosuccinate.

Powder Sopronol Propionates-Caprylate Compound. 60 and 150 Gm. canisters. A dusting powder containing 15 per cent calcium propionate, 5 per cent zinc propionate, 5 per cent zinc caprylate and 0.25 per cent propionic acid in a talc base.

Solution Sopronol Propionate-Caprylate Compound. 60 cc bottles. A dilute *n*-propyl alcohol solution containing 12.3 per cent sodium propionate, 2.7 per cent propionic acid, 10 per cent sodium caprylate and 0.1 per cent dioctyl sodium sulfosuccinate.

Licensed under U. S. patents 2,217,905 and 2,466,663, U. S. trademark 410,284.



Actions and Uses.—Propionate compound in the form of jelly is used for local application in the treatment of vulvovaginal moniliasis. Until more evidence becomes available, it is not recommended for other mycotic infections of the vulva or vagina, despite the fact that propionic acid compounds have been shown to be effective against a variety of fungous infections of the skin. It should be kept in mind that *Monilia* are occasionally found in the vaginal secretions of apparently normal women, when they are associated with *Trichomonas* infection, treatment of the latter sometimes clears up the symptoms. The relationship between these two organisms in vulvovaginitis is not yet completely understood.

Dosage.—Approximately 6 cc. of a jelly containing the propionate compound applied to the upper part of the vagina twice daily (morning and night) by means of an applicator. A single

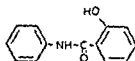
water. To determine cure, culture for *Monilia* may be taken 2 days after therapy has been discontinued. Vaginal applicators should not be used after the seventh month of pregnancy.

WYETH LABORATORIES, INC.

Propion Gel: 95 Gm. tubes with vaginal applicator. A water-miscible jelly containing 0.1 Gm. each of calcium propionate and sodium propionate in each gram.

U. S. trademark 434,356.

SALICYLANILIDE-N.F.—Salinidol (DOAX).—The structural formula of salicylanilide may be represented as follows:



Physical Properties.—Salicylanilide occurs as odorless, white or slightly pink crystals which are stable in air. It is freely soluble in alcohol, in ether, in chloroform and in benzene. It is slightly soluble in water.

Actions and Uses.—Salicylanilide is an antifungal agent useful externally in the treatment of tinea capitis due to *Microsporon audouinii*. Against that organism, in vitro, salicylanilide has approximately eight times the fungistatic power of undecylenic acid, but concentrations above 5 per cent irritate the skin. Because of its potential irritant effects on the skin, the use of salicylanilide should be restricted to ringworm of the scalp.

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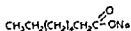
treatment. The clippings should be burned and a shampoo given after each clipping. Suitable preparations of the agent should be rubbed into the affected regions once or twice daily, 6 days each week. About 50 single daily applications (8 weeks) usually are required to completely eradicate infection.

DOAK PHARMACAL COMPANY, INC.

Ointment Salinidol 5%: 113.4 and 453.6 Gm. and 2.27 Kg. jars. An ointment containing 50 mg. of salicylanilide in each gram.

U. S. trademark 502,126

SODIUM CAPRYLATE—The sodium salt of caprylic acid—The structural formula of sodium caprylate may be represented as follows:



Physical Properties.—Sodium caprylate forms cream-colored

granules. It is freely soluble in water and sparingly soluble in alcohol.

Actions and Uses.—Sodium caprylate is applied topically in the treatment of superficial fungous infections of the skin due to trichophytons, microsporons and *Monilia albicans*. Repeated daily use has not produced irritation or sensitization of the skin.

Dosage.—Sodium caprylate is employed in the form of solution, powder or ointment, in concentrations of 10 to 20 per cent. A solution of 20 per cent is applied topically to the affected skin with a cotton applicator or by other suitable means after thorough cleansing of the involved parts.

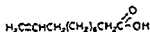
CHEMO PURO MANUFACTURING CORPORATION

Powder Sodium Caprylate: Bulk; for manufacturing use.

R. J. STRASENBURGH COMPANY

Solution Sodium Caprylate. 60 and 480 cc and 3.83 liter bottles. An aqueous solution containing 0.2 Gm. of sodium caprylate in each cubic centimeter.

UNDECYLENIC ACID-U.S.P.—"Undecylenic acid contains not less than 95 per cent of $C_{11}H_{20}O_2$ " U.S.P. The structural formula of undecylenic acid may be represented as follows:



Physical Properties.—Undecylenic acid occurs as a yellow liquid having a characteristic odor. It is almost insoluble in water but is miscible with alcohol, chloroform, ether and benzene and with fixed and volatile oils.

Actions and Uses.—Undecylenic acid is one of the more potent fatty acids employed topically as a fungistatic agent in the treatment of superficial fungus infections. Local application occasionally produces irritation and internal use for the treatment of psoriasis or other skin conditions is not established.

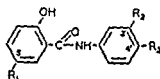
Dosage.—Undecylenic acid is applied topically in the form of a solution or emulsion in concentrations not to exceed 10 per cent. This strength may produce burning when applied to mucous membranes, therefore, it should be diluted to a 1 per cent concentration for irrigation of these structures.

WALLACE & TIERNAN, INC.

Desenex Solution Undecylenic Acid 10%: 59 and 473 cc. bottles. A solution containing 92 mg. of undecylenic acid in each cubic centimeter.

ZINCHLORUNDESAL—Salundek (New) (WALLACE & TIERNAN).—A mixture of salicylanilide-N.F., 5-chlorosalicylanilide, 5,3'-dichlorosalicylanilide and 5,4'-dichlorosalicylanilide with undecylenic

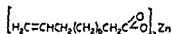
acid-U.S.P. and zinc undecylenate-U.S.P. Their structural formulas may be represented as follows:



Salicylanilide



Undecylenic acid



Zinc undecylenate

Actions and Uses.—Zinchlorundesal is effective topically in the treatment of tinea capitis caused by *Microsporon audouini*. Its use generally should be restricted to this purpose because of its potential irritant effects, although zinchlorundesal also is effective in the treatment of superficial dermatomycoses. If a cure is not obtained in 4 months, the patient should be referred for consideration of x-ray treatment.

In zinchlorundesal the irritant potentialities of the salicylanilides are minimized because lower concentrations are used, but, nevertheless, they are highly effective when combined with one another and with the relative fungistatic potentials of the chlorosalicylanilides. The fungistatic potentials of the chlorosalicylanilides are eight times that of the salicylanilides, inhibiting the growth of this micro-organism.

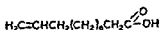
Dosage.—Zinchlorundesal is applied topically in the form of an ointment containing the stated proportions of the active ingredients. It is rubbed on the affected and adjacent areas twice daily.

WALLACE & TIERNAN, INC.

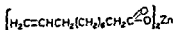
Ointment Salundek (New): 28.3 Gm. tubes and 454 Gm. jars. An ointment containing 30 mg. of salicylanilide, 20 mg. of 5-chlorosalicylanilide, 10 mg. each of 3,3'- and 5,4'-dichlorosalicylanilides, 20 mg. of undecylenic acid and 100 mg. of zinc undecylenate in each gram

U. S. trademark 572,472

ZINCUNDECATE.—Undesol (VELTEX).—A preparation containing as its active ingredients undecylenic acid-N.F. and zinc undecylenate-N.F. Their structural formulas may be represented as follows:



Undecylenic acid



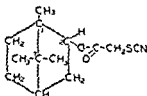
Zinc undecylenate

Actions and Uses.—Zincundecate is used for superficial dermatomycosis, epidermatophytosis including epidermatosis inguinale,

WILLIAM COOPER & NEPHEWS, INC.

Emulsion Eabin: 90 cc. bottles. An emulsion containing 0.113 Gm of benzyl benzoate, 10 mg of chlorophenothane and 20 mg. of ethyl aminobenzoate in each cubic centimeter. Stabilized with polyox-alkylene derivative of sorbitan monooleate.

ISOBORNYL THIOCYANOACETATE-TECHNICAL.—Bornate (WYETH).—The technical grade of isobornyl thiocyanacetate contains 82 per cent or more of isobornyl thiocyanacetate with other terpenes. The structural formula of isobornyl thiocyanacetate may be represented as follows:



Physical Properties.—Isobornyl thiocyanacetate-technical is a yellow, oily liquid with a terpenelike odor. It is very soluble in alcohol, benzene, chloroform and ether and practically insoluble in water.

Actions and Uses.—Isobornyl thiocyanacetate is one of the thiocyanates effective as a pediculicide. A mixture of the technical grade of this compound with dioctyl sodium sulfosuccinate in the form of an oil emulsion is useful for external application to eradicate both the adult and ova forms of *Phthirus pubis*, *Pediculus humanus capitis* and *Pediculus humanus corporis*. The compound may act as a mild primary irritant to the skin of some individuals, but there is no evidence that it acts as a sensitizing agent. It should not be applied near the eyes or to mucous membranes.

Dosage.—An oil emulsion containing 5 per cent isobornyl thiocyanacetate (technical) and 0.6 per cent dioctyl sodium sulfosuccinate is applied externally in amounts of 30 to 60 cc., depending on the site (amount of hair), worked into a lather and allowed to remain for 30 minutes. In treatment of the scalp, the hair then is combed with a fine-tooth comb and washed with a bland soap and water. On the body, the emulsion is worked well into the hair and then washed off with bland soap and water. Care must be taken that the emulsion does not remain in contact with the skin too long. More than two such applications should be avoided.

WYETH LABORATORIES, INC.

Lotion Bornate: 60 cc. and 3.785 liter bottles. An emulsion containing 5 per cent isobornyl thiocyanacetate, 0.6 per cent dioctyl sodium sulfosuccinate, in 5 per cent mineral oil, 0.6 per cent gelatin, and water.

ANTISCABIOUS AGENTS

Antiscabious agents (scabicides) are compounds that are effective against *Sarcoptes scabiei*, the animal parasite that causes scabies in man. The parasite, a mite, thrives where personal hygiene is neglected. After copulation takes place on the surface of the skin, the female mite excavates a sinuous inward-sloping burrow in the corneous layer of the skin. The eggs are laid in the burrow and, after hatching, the larvae and nymphs may exit. To be effective completely, an antiscabious agent must kill both parasites and eggs. Should the latter fail to be destroyed, repeated applications of the antiscabious agent may be necessary. The life cycle from egg to adult parasite is from 8 to 15 days. Sulphur ointment has been a time-honored scabicide.

GAMMA BENZENE HEXACHLORIDE—U.S.P.—*Gezane* (STRASBURGH) —*Kwell* (COMMERCIAL SOLVENTS) —Benzene Hexachloride. —Hexachlorocyclohexane —*Lindane* —"Gamma Benzene Hexachloride is the gamma isomer of hexachlorocyclohexane. It contains not less than 99 per cent of $C_6H_4Cl_6$ " U.S.P. The structural formula of benzene hexachloride may be represented as follows.



Physical Properties.— γ -Benzene hexachloride is a white crystalline powder with a slight, musty odor. It melts at about 112° and freezes (cryoscopic assay) not lower than 112.19° . It is soluble at 20° in 6.6 parts of acetone, 14.6 parts of alcohol, 2.5 parts of benzene, 3.2 parts of chloroform and 38 parts of ether. It is slightly soluble in ethylene glycol and practically insoluble in water.

Actions and Uses.— γ -Benzene hexachloride is applied to the skin as a scabicide and pediculicide. Because the drug is highly toxic its application to man must be supervised by a physician. Animal experiments indicate that it may be absorbed readily through the skin. However, it may be used safely in concentrations up to 1 per cent if prolonged or repeated application is avoided. A single application usually is adequate to eliminate the active parasites; a second or third application may be required on rare occasions. The nits are not dissolved. It is somewhat irritating to mucous membranes and should not be permitted to come in contact with the eyes. The presence of secondary infection does not interfere with its use, but other appropriate measures may be required to control such complications.

Dosage.— γ -Benzene hexachloride, in concentrations up to 1 per cent, is applied topically as a lotion or ointment. Usually not more

towel should be worn over the head for 1 hour after application and, in the case of female patients, it may be advisable to cut the hair before treatment. A small brush may be used to facilitate thorough application to the scalp. All clothing and bed linen should be sterilized thoroughly by boiling to prevent reinfection; wool garments should be dry cleaned. Patients should be instructed not to bathe or wash the hands or hair for at least 24 hours after treatment. A second application may be made after 1 week if the first is not successful. It is recommended that γ -benzene hexachloride be applied no more than three times as repeated use may irritate the skin.

COMMERCIAL SOLVENTS CORPORATION

Lotion Kwell 1%: 60 and 473 cc bottles. A lotion containing 10 mg. of γ -benzene hexachloride in each cubic centimeter.

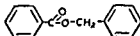
Ointment Kwell 1%: 56.7 Gm. tubes and 454 Gm. jars. An ointment containing 10 mg. of γ -benzene hexachloride in each gram.
U. S. trademark 503,133.

R. J. STRASSENBURGH COMPANY

Liquid Gexano 1%: 59.14 and 473 cc and 3.78 liter bottles. A lotion containing 10 mg. of γ -benzene hexachloride in each cubic centimeter.

Ointment Gexano 1%: 21.26 Gm. tubes and 454 Gm. jars. An ointment containing 10 mg. of γ -benzene hexachloride in each gram.

BENZYL BENZOATE-U.S.P.—*Berylate* (BROWN).—*Vanzoate* (VANZELT & BROWN).—"Benzyl benzoate contains not less than 99 per cent of $C_{14}H_{12}O_2$ " U.S.P. The structural formula of benzyl benzoate may be represented as follows:



Physical Properties—Benzyl benzoate is a clear, colorless, oily liquid having a slight aromatic odor and a sharp, burning taste. It is insoluble in water and in glycerin. It is miscible with alcohol, with ether and with chloroform. It congeals at a temperature not below 18°.

recommended Application occasionally is followed by a slight,

Dosage.—A 10 to 30 per cent lotion or emulsion of benzyl benzoate is applied with a swab or brush over the entire body surface (*except the face*) while the skin is still damp immediately following scrubbing of the lesions in a 10-minute bath in soap and warm water. Care should be taken to ensure application to and around

four hours later, clean clothing is put on after a warm soaking bath. A second or third treatment following the same routine should be carried out if necessary to eradicate the parasite. Secondary pyogenic infections do not contraindicate treatment, but should be treated appropriately.

THE BLUE LINE CHEMICAL COMPANY

Lotion Benzyl Benzoate: 473 cc and 3 78 liter bottles. An oil-in-water emulsion containing about 28 per cent w/w of benzyl benzoate, 0.5 per cent triethanolamine and 2 per cent oleic acid.

GEORGE A. BREON & COMPANY

Lotion Benylate: 118 cc. and 473 cc bottles. An oil-in-water emulsion containing 25 per cent of benzyl benzoate and approximately 2 per cent of triethanolamine stearate. The product is required to be labeled as Modified Benzyl Benzoate Lotion because it differs from the official benzyl benzoate lotion-*USP* essentially in the emulsifying agent used in its preparation.

VANPELT & BROWN, INC

Lotion Vanzoate: 118 cc and 3 78 liter bottles. A suspension containing 0.28 Gm. of benzyl benzoate in each cubic centimeter. Preserved with 0.009 per cent *n*-butyl *p*-hydroxybenzoate.

U S trademark 415,423

VELTEX COMPANY

Lotion Benzyl Benzoate: 450 cc. and 3.84 liter bottles. An oil-in-water emulsion containing 25 per cent v/v of benzyl benzoate, 0.5 per cent triethanolamine and 2 per cent oleic acid.

BENZYL BENZOATE-CHLOROPHENOTHANE-ETHYL AMINO-BENZOATE.—For monograph see the section on antipedicular agents

...ing powdered
...m) with a hy-
...ctuous, yellow-
ish green mass.

Actions and Uses.—Pyrethrum applied as an ointment is effective in the treatment of scabies. The ointment penetrates the burrows and kills both the mites and the eggs, and, except in rare instances, it does not produce dermatitis with resultant exfoliation.

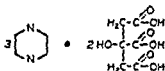
Dosage.—Pyrethrum is applied as an ointment to the entire body following a thorough cleaning with soap and water. Further applications are made on at least 3 or 4 successive days. In most cases it is necessary to continue the treatment for 5 to 7 days, and in obstinate cases for a longer time. Pyrethrum should not be prescribed for patients who are sensitive to pyrethrum flowers.

UPSHER SMITH COMPANY

Ointment Pyrethrum: 100 Gm jars. An ointment containing 27 per cent of the active extract (representing 0.75 per cent of pyrethrine I and II) in an ointment base composed of hydrous wool fat, petrolatum and paraffin.

VERMIFUGAL AGENTS

PIPERAZINE CITRATE.—Antepar Citrate (BURROUGHS WELLCOME).—Multifuge Citrate (BLUE LINE).—Piperazine citrate is formed by the reaction of an excess of piperazine hexahydrate with citric acid. The product, which is not isolated from solution, is believed to have the following structural formula



Actions and Uses.—Piperazine citrate is useful as an anthelmintic for the treatment of infections caused by pinworms (*Enterobius vermicularis*; *Oxyuris vermicularis*) and roundworms (*Ascaris lumbricoides*). The drug is relatively nontoxic to humans and usually produces no side effects when administered in anthelmintic doses. The ingestion of excessively large amounts may produce urticaria or vomiting, blurred vision and general muscular weakness, which disappear when the drug is discontinued. Excessively prolonged or repeated treatment should be avoided.

Dosage.—Piperazine citrate is administered orally. The dosage is expressed, in terms of the hydrous base, piperazine hexahydrate. For children and adults the daily dose may be calculated on the basis of 50 mg per kilogram of body weight, but this should be limited to not more than 2 Gm daily per patient. The calculated total daily dosage usually is divided into two equal doses administered morning and night. For pinworms, treatment is administered either as a single course for 14 days or for 7 days followed by a rest period of 1 week, with a second course for 7 days. For ascariasis, a single course of 3 to 7 days usually is adequate. Appropriate precautions should be taken to prevent reinfection, especially in the treatment of pinworms.

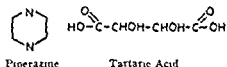
THE BLUE LINE CHEMICAL COMPANY

Syrup Multifuge Citrate: 118.3 and 473 cc. and 3.78 liter bottles. A syrup containing the equivalent of 0.1 Gm. of piperazine hexahydrate as the citrate in each cubic centimeter. Preserved with 0.1 per cent methylparaben and 0.1 per cent sodium benzoate.

BURROUGHS WELLCOME & COMPANY, INC.

Syrup Antepar Citrate: 118.3 and 473 cc. and 3.78 liter bottles. A syrup containing the equivalent of 0.1 Gm. of piperazine hexahydrate as the citrate in each cubic centimeter. Preserved with 0.1 per cent methylparaben and 0.1 per cent sodium benzoate.

PIPERAZINE TARTRATE.—Piperat Tartrate (LINCOLN).—Piperazine tartrate is formed by the reaction of an excess of piperazine hexahydrate with tartaric acid. The structural formula for piperazine and for tartaric acid may be represented as follows:



Actions and Uses.—Piperazine tartrate is employed for the same purposes as other salts of the base. See the monograph on piperazine citrate.

Dosage.—Piperazine tartrate is administered orally and, like other salts of the base, the dosage is expressed in terms of the base, piperazine hexahydrate.

LINCOLN LABORATORIES, INC.

Solution Piperat Tartrate (*Oral*): 473 cc. bottles. A solution containing the equivalent of 0.1 Gm. of piperazine hexahydrate as the tartrate in each cubic centimeter. Preserved with 0.08 per cent methylparaben, 0.02 per cent propylparaben and 0.1 per cent sodium bisulfite.

5

Systemic Anti-infectives

Systemic anti-infectives include therapeutic agents administered internally, orally or parenterally to combat infection. Thus the

they are administered internally. Others that may be used, both locally and internally, are included in this chapter or the chapter on local anti-infectives on the basis of the principal method of application.

ANTIBACTERIAL AGENTS

Aminosalicylic Acid Derivatives

AMINOSALICYLIC ACID—U.S.P.—*Para-Pas (GOLD LEAF)*—*Para-sal (PANRAY)*—*Propasa (SHARP & DOHME)*—*Para-Aminosalicylic Acid—PAS*—"Aminosalicylic Acid contains not less than 98.5 per cent of $C_7H_7NO_3$, calculated on the dried basis" *U.S.P.* The structural formula for aminosalicylic acid may be represented as follows:



Physical Properties—Aminosalicylic acid is a white or nearly white bulky powder which is odorless or has a slight acetous odor. It melts with decomposition between 135 and 140°. One part is soluble in 21 parts of alcohol and in 500 parts of water. At 25°, 0.2 Gm dissolves in 100 cc of water and 4.75 Gm dissolves in 100 cc of alcohol. One gram dissolves in 10 cc of 10 per cent sodium bicarbonate to give a clear solution with no more than a faint yellow color. A saturated aqueous solution has a pH between 3.2 and 3.7.

Actions and Uses—Aminosalicylic acid has *in vitro* and *in vivo* action against the tubercle bacillus, although it is less potent than the streptomycins. It is used principally as a supplement to these antibiotics, not only because it may produce some addition of effects, but also because the combination may postpone the development of bacterial resistance. Aminosalicylic acid may be indicated alone in tuberculous infections in which the bacilli have

become resistant to streptomycin and dihydrostreptomycin or where, for any reason, these antibiotics may be contraindicated. Resistance to aminosalicylic acid usually develops slowly. Aminosalicylic acid alone may be indicated, also, in infections that are deeply entrenched, especially when surgery is anticipated later, and it is desirable to reserve the streptomycin drugs for that time.

The drug is absorbed well from the alimentary tract, producing blood levels that usually are maintained for 4 hours. Excretion in the urine is rapid and nearly complete. Epigastric discomfort, anorexia, nausea and vomiting are frequently troublesome toxic manifestations. Occasionally, soft stools or, less frequently, diarrhea occurs. In other respects the drug has been harmful only rarely to human beings, but dermatoses and drug fever have been reported. Small initial doses; smaller, more frequent subsequent doses; simultaneous administration of 5 to 10 cc of aluminum hydroxide gel and the routine administration with meals may limit the gastrointestinal disturbances.

Dosage.—Aminosalicylic acid may be given in the form of tablets or capsules, coated granules or in solution. The recommended daily dose is 8 to 16 Gm, given orally in four or more doses.

AMERICAN PHARMACEUTICAL COMPANY

Tablets Para-Aminosalicylic Acid. 0.5 Gm. plain and specially coated brown

GOLD LEAF PHARMACEUTICAL COMPANY, INC.

Powder Para-Pas: 113.4, 226.7 and 454 Gm and 2.27 Kg. bottles, and 11.3 and 22.7 Kg drums for compounding use

Tablets Para-Pas: 0.5 Gm

MERCK & CO., INC.

Powder Para-Aminosalicylic Acid: 50 and 500 Gm. bottles; 2.5 Kg fiber drums.

THE PANRAY CORPORATION

Powder Parasal: 113.4, 226.8 and 453.6 Gm. bottles. Bulk, 11.34 and 22.68 Kg drums for compounding use.

Tablets Parasal: 0.5 Gm

Tablets Parasal (Buffered): 0.5 Gm Buffered with 11.5 per cent calcium carbonate and 7.7 per cent dihydroxy aluminum aminoacetate.

U. S. trademarks 537,496 and 585,718

PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets p-Aminosalicylic Acid. 0.5 Gm.

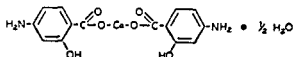
SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Effervescent Tablets Propasal: 1 Gm. Each tablet contains 1 Gm.

of aminosalicilic acid and 0.7 Gm of sodium bicarbonate. When dissolved in water, each tablet yields 1.38 Gm. of sodium aminosalicylate

U. S. trademark 536,152.

represented as follows



Physical Properties.—Calcium aminosalicylate occurs as white to cream-colored crystals or powder. It is odorless and has an alkaline, slightly bittersweet taste. It is somewhat hygroscopic. Its solutions decompose slowly and darken in color. One gram dissolves in about 7 cc of water, in about 6 cc of methanol, in about 12 cc of acetone and in about 30 cc of alcohol.

Actions and Uses.—Calcium aminosalicylate shares the actions and uses of aminosalicilic acid and sodium aminosalicylate. (See the monograph on aminosalicilic acid.) Calcium aminosalicylate has no established advantage over the sodium salt, except that it can be administered to patients on a sodium-restricted diet. Its therapeutic activity is considered equal to that of sodium aminosalicylate. The incidence of gastric intolerance or other side effects has not been shown conclusively to be less with the calcium than with the sodium salt.

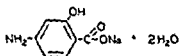
larger than the usual dose of the acid to provide an equivalent amount of the drug, whereas the hydrated sodium salt would require a 38 per cent larger dose than the acid. A total daily dose of 15 Gm of the sodium aminosalicylate yields about 1.6 Gm. of sodium, which makes the sodium salt unsuitable for aminosalicilic acid therapy in patients who are required to restrict sodium intake.

FINE CHEMICALS DIVISION, AMERICAN CYANAMID COMPANY

Powder Calcium Para-Aminosalicylate. Bulk, for manufacturing or compounding use.

SODIUM AMINOSALICYLATE-U.S.P.—*Para Pas Sodium* (GOLD LEAF).—*Parasal Sodium* (PARAY).—*Parasa Sodium* (SMITH-

DORSLY).—Pasem Sodium (MASSENGILL).—Pasmed Sodium (INTERMEDICO).—Sodium Para-Aminosalicylate.—“Sodium Aminosalicilate contains not less than 98 per cent and not more than 101 per cent of $C_7H_6NNaO_3$, calculated on the anhydrous basis.” U.S.P. The structural formula for sodium aminosalicilate may be represented as follows:



Physical Properties.—Sodium aminosalicilate is a white to pale yellow, practically odorless, crystalline powder. It is freely soluble in water, sparingly soluble in alcohol and practically insoluble in ether. One gram dissolves in 50 cc of water to give a clear solution which is colorless or nearly so. The solution has a pH between 7.0 and 7.5.

Actions and Uses.—See the monograph on aminosalicilic acid.

Dosage.—3 Gm. five times daily for a total dose of 15 Gm. every 24 hours. The duration of treatment is the same as with aminosalicilic acid.

AMERICAN PHARMACEUTICAL COMPANY

Tablets Sodium Para-Aminosalicylate: 0.5 Gm.

GOLD LEAF PHARMACEUTICAL COMPANY, INC.

Powder Para-Pas Sodium: 113.4, 226.7 and 454 Gm. and 2.27 Kg. bottles, and 11.3 and 22.7 Kg. drums for compounding use.

Tablets Para-Pas Sodium: 0.69 Gm.

INTERMEDICO CORPORATION

Tablets Pasmed Sodium: 0.5 Gm.

S. E. MASSENGILL COMPANY

Capsules Pasem Sodium: 0.5 Gm.

THE PANRAY CORPORATION

Powder Parasol Sodium: 113.4, 226.8 and 453.6 Gm. bottles Bulk; 11.34 and 22.68 Kg. drums for compounding use.

Tablets Parasol Sodium: 0.69 Gm.

U. S. trademark 585,718

PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Sodium p-Aminosalicylate: 0.5 Gm.

SMITH-DORSEY, DIVISION OF THE WANDER COMPANY

Capsules Pasara Sodium: 0.5 Gm.

Powder Pasara Sodium: 454 Gm. bottles and 11.34 Kg. containers.

Tablets Pasara Sodium: 0.5 Gm.

is comparable to that in the blood. The drug passes readily through the meningeal barrier and is well distributed in all of the various body fluids. There is no evidence that the drug accumulates in the tissues or that tolerance develops when administration of the recommended dosage is continued.

Intramuscular injection produces plasma concentrations approximately equal to those obtained with the same dosage administered orally. Following injection, the drug is excreted somewhat more rapidly in the urine. Transient, local pain at the site of injection may be encountered. Intramuscular injection of the drug is therapeutically equivalent to oral administration and should be employed whenever the latter route is not feasible, as in coma caused by tuberculous meningitis or during the early postoperative period following pulmonary resection. An injectable solution also may be employed topically for tuberculous empyema or effusion.

Experimental animal studies indicate a wide margin of safety between the effective and toxic doses of isoniazid. Toxic doses in animals produce reversible symptoms, which include anorexia, weight loss (from loss of appetite), liver damage and signs of central nervous system stimulation manifested by tremor, ataxia, rapid respiration, bradycardia and, in some instances, convulsions. In laboratory animals, phenobarbital diminishes the convulsive action of isoniazid and forced feeding has mitigated the hepatic damage produced by isoniazid in these animals. Toxic doses also produce some kidney damage in animals. Since isoniazid is excreted chiefly by the kidney, it should be given with caution and in the lowest recommended effective dose where renal damage is expected or known to exist. Renal tuberculosis should not be treated unless adequate facilities are available for estimating blood levels of isoniazid.

The toxic effects observed in human beings include vertigo, constipation, twitching of the lower extremities, drowsiness, head-

aches, and numbness of the urinary
not have
cases of
late anti-

convulsant medication before and during isoniazid therapy.

Dosage—Isoniazid is administered orally or intramuscularly in the recommended daily dosage of 3 to 5 mg per kilogram of body weight, divided into equal doses every 12 hours. This dosage should be exceeded only with caution and when adequate facilities are available to detect toxic symptoms. In patients seriously ill, such as those suffering from tuberculous meningitis or miliary tuberculosis, it is advisable to give a maximum total daily dosage of 15 mg per kilogram of body weight for a period of 2 to 3 weeks. Signs of a toxic reaction should be watched for.

Isoniazid may be used concurrently with streptomycin or dihydrostreptomycin. Either of these drugs should be administered intermittently twice weekly or every 3 days in doses of 1 Gm for adults or 20 mg per kilogram of body weight for children,

given intramuscularly. Concomitant use of isoniazid with daily 1 Gm doses of a streptomycin drug should be restricted to acute forms of tuberculosis and limited to a period of 1 to 2 weeks until there is more information concerning the side effects that may result from this method of therapy.

For intramuscular injection, a solution containing 100 mg per cubic centimeter should be administered so as to provide the same dosage as that indicated by the oral route. The same concentration can be applied topically in 10 cc amounts three times weekly for the local treatment of tuberculous empyema or effusion.

AMERICAN PHARMACEUTICAL COMPANY

Tablets Isoniazid. 50 mg.

THE BOWMAN BROS. DRUG COMPANY

Tablets Isoniazid. 50 mg

ENDO PRODUCTS, INC.

Tablets Niazidrin: 50 and 100 mg

U S trademark 398,543

HOFFMANN-LA ROCHE, INC.

Tablets Rimifon: 50 and 100 mg.

U S patent 2,596,069 U S trademark 563,939

KEITH-VICTOR PHARMACAL COMPANY

Tablets Zinadon: 50 and 100 mg.

THE WM. S. MERRELL COMPANY

Tablets Tyvid. 50 mg

NEPERA CHEMICAL COMPANY, INC.

Tablets Pyrizidin: 50 and 100 mg.

U S trademark 593,838

THE PANRAY CORPORATION

Tablets Isoniazid: 50 and 100 mg.

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

Tablets Cotinazin: 50 mg.

PREMO PHARMACEUTICAL LABORATORIES, INC.

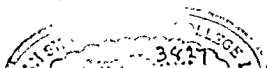
Tablets Nicoride: 50 and 100 mg.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Capsules Nydraxid. 50 and 100 mg.

Solution Nydraxid (*Intramuscular*): 10 cc. vials. A solution containing 100 mg. of isoniazid in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Syrup Nydraxid: 473 cc. bottles. A flavored syrup containing



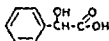
10 mg. of isoniazid in each cubic centimeter. Preserved with 0.1 per cent of sodium benzoate.

Tablets Nydravid: 50 and 100 mg.

U. S. patent 2,596,069. U. S. trademark 562,900.

Mandelic Acid Derivatives

MANDELIC ACID.—Racemic Mandelic Acid—The structural formula of mandelic acid may be represented as follows:



Physical Properties.—Mandelic acid occurs as white crystals or crystalline powder. It is odorless or has a slight aromatic odor; it darkens and decomposes gradually on exposure to light. One gram dissolves in about 6.5 cc. of water at 25°; it is freely soluble in alcohol.

Actions and Uses.—Mandelic acid is a substance that is not metabolized; when administered by mouth, it is excreted unchanged in the urine. If the pH of the urine is kept at 5.5 or less, mandelic acid is bactericidal or bacteriostatic against *Escherichia coli*, *Aerobacter aerogenes*, *Streptococcus faecalis* and organisms of the Proteus, Pseudomonas, Alcaligenes, Salmonella and Shigella groups.

in the urine; renal irritation and serious acidosis may result from retention of the acid.

Dosage.—The usual dosage is 3 Gm. four times a day of either the free acid or the sodium or ammonium salt. An additional acidifying agent usually is required when the sodium salt is employed.

MALLINCKRODT CHEMICAL WORKS

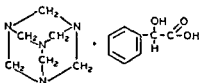
Powder Mandelic Acid: Bulk; 454 Gm. containers for compounding use.

MERCK & CO., INC.

Powder Mandelic Acid: Bulk; 453 Gm. bottles for compounding use.

Methenamine Compounds

METHENAMINE MANDELATE-U.S.P.—Mandelamine (NEPERA).—Hexamethylenamine Mandelate—Hexamethylenetetramine Mandelate—"Methenamine Mandelate contains not less than 46 per cent of methenamine ($C_6H_{12}N_4$) and not more than 50 per cent of mandelic acid ($C_8H_8O_3$), calculated on the dried basis." *U.S.P.* The structural formula of methenamine mandelate may be represented as follows.



Physical Properties.—Methenamine mandelate is a white, crystalline powder with a sour taste and practically no odor. It melts between 127 and 130°. It is very soluble in water. One part of methenamine mandelate is soluble in about 10 cc. of alcohol, 20 cc. of chloroform and 350 cc. of ether. The pH of a 1 per cent solution is between 4.2 and 4.4.

Actions and Uses.—Methenamine mandelate combines the actions of two established urinary antiseptics, methenamine and mandelic acid. The compound acts to some extent as an acidifying agent. However, in those infections caused by urea-splitting bacteria, preliminary acidification of the urine over a period of 24 to 36 hours prior to beginning therapy is essential to provide a urinary pH

to most other commonly employed antibacterial agents. Comparison of the bactericidal and bactericidal action of methenamine mandelate with that of methenamine and mandelic acid shows that the compound is more effective than either of the two individual components.

otherwise susceptible bacterial strains.

Methenamine mandelate seldom is associated with untoward effects, in therapeutically effective amounts, gastric disturbance is infrequent and other toxic manifestations are relatively rare. It is contraindicated in the presence of renal insufficiency.

Dosage.—Methenamine mandelate is administered orally. The average dose for adults is 0.75 to 1 Gm. three times daily; for chil-

dren over 5 years of age, 0.25 Gm. three times daily; for infants less than 1 year of age, 0.25 Gm. twice daily.

NEPERA CHEMICAL COMPANY, INC.

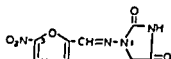
Tablets Mandelamine: 0.25 Gm. enteric coated.

Tablets Mandelamine Halfgrams: 0.5 Gm. enteric coated.

U. S. patent 2,124,321. U. S. trademark 347,322.

Nitrofurantoin Derivatives

NITROFURANTOIN.—Furadantin (EATON).—N-(5-Nitro-2-furylidene)-1-aminohydantoin.—The structural formula of nitrofurantoin may be represented as follows.



Physical Properties.—Nitrofurantoin is a yellow, bitter powder with a slight odor. It decomposes at 258 to 262°. It is very slightly soluble in alcohol and practically insoluble in ether and water.

Actions and Uses.—Nitrofurantoin, a nitrofuran derivative, exhibits a wide spectrum of antibacterial activity against both gram-positive and gram-negative micro-organisms. It is both bacteriostatic and bactericidal to the majority of strains of *Escherichia coli*, *Micrococcus* (Staphylococcus) *pyogenes albus* and *aureus*, *Streptococcus pyogenes*, *Aerobacter aerogenes* and *Paracolonobacterium* species. The drug is less effective against *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Alcaligenes faecalis* and *Corynebacterium* species; many strains of these organisms may be resistant to it, however, bacterial resistance to other anti-infective agents is not usually accompanied by increase in resistance of the organisms to nitrofurantoin. The drug does not inhibit fungi or viruses.

Nitrofurantoin is useful by oral administration for the treatment of bacterial infections of the urinary tract and is indicated in pyelonephritis, pyelitis and cystitis caused by bacteria sensitive to the drug. It is not intended to replace surgery when mechanical

occasionally produces nausea and emesis; however, these reactions may be obviated by slight reduction in dosage. An occasional case of sensitization has been noted, consisting of a diffuse, erythematous, maculopapular eruption of the skin. This has been controlled readily by discontinuing administration of the drug. Animal studies, using large doses administered over a prolonged period, have revealed a decrease in the maturation of spermatozoa, but this effect is reversible following discontinuance of the drug. Until more is known concerning its long-term effects, blood cell studies should be made during therapy. Frequent or prolonged treatment is not advised until the drug has received more widespread study. It is contraindicated otherwise in the presence of anuria, oliguria or severe renal damage.

Dosage.—Nitrofurantoin is administered orally in an average total daily dosage of 5 to 8 mg per kilogram (2.2 to 3.6 mg per pound) of body weight. One-fourth of this amount is administered four times daily—with each meal and with food at bedtime, to prevent or minimize nausea. For refractory infections caused by organisms such as *Proteus* and *Pseudomonas* species, the total daily dosage may be increased to a maximum of 10 mg per kilogram (4.5 mg per pound) of body weight. If nausea is severe, the dosage may be reduced. Medication should be continued for at least 3 days after sterility of the urine is achieved.

EATON LABORATORIES

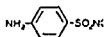
Oral Suspension Furadantin: 118 cc bottles. A flavored suspension containing 5 mg. of nitrofurantoin in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

Tablets Furadantin: 50 and 100 mg.

U. S. patent 2,610,181. U. S. trademark 569,968.

Sulfonamide Compounds

The sulfonamide group is a synthetic chemical group that is derived from the sulfonamide group. It is a synthetic chemical group that is derived from the sulfonamide group. It is a synthetic chemical group that is derived from the sulfonamide group.



In addition, they may carry a single substituent on the *p*-amino group.

The major effect of the sulfonamides as a group is to prevent synthesis by bacteria of pteroyl compounds. Pteroyl compounds are required by many species as growth factors. Sulfonamide therapy must be administered in dosages that will maintain concentrations sufficient to prevent the utilization of available *p*-aminobenzoic acid in the body. Insufficient therapy may result in an increase of

resistant pathogenic forms. High concentrations may be bactericidal to susceptible invading organisms, but the major effect of sulfonamides upon micro-organisms usually is bacteriostatic. The antisulfonamide action of *p*-aminobenzoic acid is of special importance because many local anesthetics (procaine is a good example) are esters of *p*-aminobenzoic acid and are metabolized partly to the parent substance when injected into the tissues.

The choice of the sulfonamide compound to be used in the control of known infections should be based on bacteriologic diagnosis, knowledge of the experimental therapeutic value of these drugs, their pharmacologic properties in man, their clinical efficacy and, finally, the variety, the frequency and the severity of the toxic reactions that each may produce.

Sulfonamides are not the drugs of choice for the treatment of anaerobic streptococcic infections, enterococcic infections, rheumatoid arthritis, active rheumatic fever, subacute bacterial endocarditis, tularemia, undulant fever, tuberculosis, lymphogranuloma inguinale, the common cold, measles, influenza and pemphigus. Sulfadiazine and sulfamerazine are drugs of choice for meningococcic meningitis.

If there is an antibiotic that is effective for the treatment of a given infection, it usually should be employed in moderate or severe cases, either alone or in conjunction with a therapeutically active sulfonamide.

Experience gained in World War II indicates that the use of crystalline sulfonamides and of sulfonamide ointments, creams and lotions as topical agents was not successful in the management of wound infection or in treatment of infections of the skin or mucous membrane. Use of sulfonamides as topical applications in

Toxicity.—Sulfonamide compounds produce many and various toxic reactions. Hence, patients who are being treated with these drugs should be examined at frequent intervals in order that the early signs of toxicity may be noted and the drug stopped.

The sulfonamides currently recommended produce fewer toxic reactions than did sulfanilamide, sulfapyridine or sulfathiazole. Nausea, vomiting, dizziness and cyanosis are uncommon and acidosis does not occur. Mental disturbances and acute psychoses have been observed in patients given one or a mixture of the pyrimidine derivatives.

Mild peripheral neuritis, drug fever, skin rashes of many morphologic types, injection of the conjunctiva and sclera, petechiae and purpura have occurred. Acute toxic hepatitis is uncommon but has been reported, acute hemolytic anemia is rare. Granulocytopenia has been observed early and late in the course of treatment with pyrimidine derivatives, and agranulocytosis occurs most frequently between the tenth and twenty-first days of therapy. Microscopic and gross hematuria with or without crystalluria may occur during treatment with the pyrimidine derivatives, especially when the patient's intake of fluids has been low. Com-

plete cessation of renal function, beginning with oliguria and progressing to anuria accompanied by azotemia, is the most common serious toxic reaction to the individual pyrimidine derivatives; it occurs less frequently when mixtures of the pyrimidine derivatives are administered. Because of the possibility that renal lesions may be produced, fluids adequate to produce a daily urinary output of at least 1,000 cc., should be given to patients receiving any pyrimidine derivatives. Alkalinization of the urine during treatment with sulfadiazine, sulfamerazine, and/or sulfamethazine, decreases the likelihood of renal complications. When serious toxic reactions develop, the sulfonamide should be stopped and fluids forced in order that the drug may be eliminated as rapidly as possible. However, when oliguria or anuria is present, fluids should not be administered to the point of producing edema. In order to avoid photosensitization, all patients receiving sulfonamides should be kept out of the sun and should not receive ultraviolet radiation.

When sulfonamide drugs are being used it is always desirable

venously the sodium ions are split off promptly, leaving the

pounds is intravenous injection as 5 per cent solutions in sterile pyrogen-free distilled water or sterile pyrogen-free isotonic sodium chloride solution.

ger of producing a chemical necrosis of the tissues. It has been

The use of solutions of the sodium salts of sulfonamide compounds is indicated in severe infection in which it is desired to obtain promptly adequate blood concentrations of these drugs, for patients who by reason of disturbances of the gastro-intestinal tract, such as vomiting, are not obtaining proper concentrations of these drugs when they are given orally and, finally, for patients in whom the absorption of these drugs is poor or whose rate of conjugation is such that adequate concentrations cannot be obtained in the blood and tissues by other routes of administration.

With the exception of patients ill with severe infections, and those to whom these drugs cannot be given by the oral route, it is rarely necessary to administer intravenous injections of solution of the sodium salts of the sulfonamides more than once or

istration of the parent drug by the oral route should be commenced

Aside from the damage to tissues that may result from the careless administration of the sodium salts of these sulfonamides by the intravenous route, the toxic reactions noted in the course of their administration are those that occur when the parent sulfonamide is administered by the oral route.

Pyrimidine Derivatives

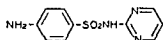
When sulfadiazine is administered orally, its absorption from the gastro-intestinal tract is slower and less complete than that of sulfanilamide. Sulfamethazine resembles sulfadiazine in respect to absorption, but sulfamerazine is absorbed more rapidly and completely than either. As sulfamerazine is excreted more slowly than sulfadiazine or sulfamethazine, smaller doses produce blood concentrations comparable to those obtained with either of the other two pyrimidine derivatives. All three of these agents are excreted primarily in the urine, where they are found in the free and conjugated forms. The renal clearance of sulfamethazine is similar to that of sulfamerazine and about half that of sulfadiazine, and when renal function is subnormal, they accumulate in the blood. Acetylated sulfamerazine is the most soluble of the three drugs, but sulfamethazine, when absorbed, is conjugated to the acetyl derivatives more easily than are the other two compounds. All three pass over into the spinal fluid in fair concentrations, and the concentrations increase when the meninges are inflamed. None of

obtained easily with all three of the drugs. Each is bound to the blood proteins to a different degree, sulfamethazine having the highest binding power. All three pyrimidine derivatives penetrate the red blood cells.

Sulfadiazine, sulfamerazine and sulfamethazine, singly or in mixtures, are effective in hemolytic streptococcal infections caused by Lancefield's Group A organisms and in pneumococcal, meningococcal and staphylococcal infections. Urinary tract infections produced by *E. coli*, *A. aerogenes*, *B. proteus*, *Ps. aeruginosa* and systemic infections caused by *K. pneumoniae* or *H. influenzae* may also respond. These sulfonamides also are beneficial in the treatment of bacillary dysentery and early trachoma and may have value in the treatment of pyoderma, follicular conjunctivitis, the diazines may be used also in the treatment of syphilis, and in the prophylaxis of rheumatic fever. For

carriers of meningococcus, it is usually sufficient to administer 2 Gm. of sulfadiazine per day for 2 days. Actinomycosis or gas gangrene may be treated with sulfadiazine, sulfamerazine or sulfamethazine in conjunction with a potent antibiotic.

SULFADIAZINE-U S P. — 2-Sulfanilamidopyrimidine. — N^1 -2 — Pyrimidylsulfanilamide — "Sulfadiazine, dried at 105° for 2 hours, contains not less than 99 per cent of $C_{10}H_{10}N_4O_2S$." *U.S.P.* The structural formula of sulfadiazine may be represented as follows:



Physical Properties.—Sulfadiazine occurs as a white, odorless, tasteless, crystalline powder. It may be recrystallized from hot water to yield long, flat needles. It is soluble in both alkaline and mineral acid solutions, sparingly soluble in alcohol, acetone and water, insoluble in ether and chloroform.

Actions and Uses.—See the general statement on sulfonamides

coccic pneumonia, severe hemolytic streptococcus infections, severe staphylococcic infections or meningococcic meningitis, the initial dose should be 0.1 Gm per kilogram of body weight. Then, if the patient is suffering from pneumococcic pneumonia, 1 Gm should be given every 4 hours day and night until the temperature has been normal for 72 hours. The drug then may be withdrawn. In severe streptococcic, staphylococcic and meningococcic infections, subsequent doses after the initial doses are 1 to 1.5 Gm. every 4 hours day and night until the temperature has been normal for 5 to 7 days. At this time the drug may be either stopped or continued in smaller doses until the complete recovery of the patient is assured.

In children suffering from pneumonia the initial oral dose should be based on 0.1 to 0.15 Gm per kilogram of body weight, and subsequent doses of one-fourth of the initial dose should be given at intervals of 6 hours until the temperature has been normal for at least 4 days. In staphylococcic pneumonia, 5 to 7 days of treatment should be continued until cure is effected.

In mild or moderately severe hemolytic streptococcus infections, the dosage suggested is an initial oral dose of 0.05 Gm per kilogram of body weight, followed by one-third of the initial dose given every 4 hours day and night by mouth until the temperature has been normal for 3 to 5 days. All of the above dosages should be controlled, if possible, by determination at frequent intervals of the concentration of the drug in the blood (see Bratton and Marshall method under *Toxicity* in the general statement on

sulfonamide compounds). In severe streptococcal, staphylococcal, meningococcal or Friedlander's bacillus infections, it is necessary during the febrile period to obtain and maintain concentrations of approximately 15 mg of sulfadiazine per 100 cc. in the patients' blood; it is rarely necessary or advisable to exceed this concentration. In mild or moderately severe streptococcus infections, concentrations of 5 to 10 mg. of the drug per 100 cc. of blood are usually satisfactory. In acute gonococcus urethritis in adults, the initial dose is 4 Gm, to be followed by 1 Gm. every 6 hours for 5 days.

There may be a high incidence of oliguria, hematuria and anuria following sulfadiazine therapy under conditions where the output of urine cannot be maintained above 600 or 800 cc. per day, as in tropical climates or where a shortage of water exists. It is recommended that where such complications are encountered, an initial dose of 4 Gm. of sodium bicarbonate together with the initial dose of sulfadiazine be administered, followed by 2 Gm. of sodium bicarbonate every 4 hours regardless of the dosage of sulfadiazine being employed. In the management of complications resulting from the toxic action of sulfadiazine on the kidneys, the administration of even larger doses of alkali, such as 3 or 4 Gm. every 4 hours, may be helpful.

ABBOTT LABORATORIES

Dulcet Tablets Sulfadiazine: 0.15 and 0.3 Gm
U. S. trademark 500,527.

Powder Sulfadiazine: 113 and 454 Gm bottles.

Tablets Sulfadiazine: 0.5 Gm.

AMERICAN PHARMACEUTICAL COMPANY, INC.

Tablets Sulfadiazine: 0.5 Gm.

THE BOWMAN BROS. DRUG COMPANY

Tablets Sulfadiazine: 0.5 Gm.

Hexett Tablets Sulfadiazine: 65 mg.

BREWER & COMPANY, INC.

Tablets Sulfadiazine: 0.5 Gm.

BUFFINGTON'S, INC.

Tablets Sulfadiazine: 0.5 Gm.

COLE CHEMICAL COMPANY

Tablets Sulfadiazine: 0.5 Gm.

THE EVRON COMPANY, INC.

Tablets Sulfadiazine: 0.5 Gm.

KEITH-VICTOR PHARMACAL COMPANY

Tablets Sulfadiazine: 0.5 Gm.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY
Powder Sulfadiazine: 113 and 454 Gm packages.

Tablets Sulfadiazine: 0.5 Gm.

ELI LILLY & COMPANY

Tablets Sulfadiazine: 65 mg. and 0.5 Gm.

MALLARD, INC.

Tablets Sulfadiazine: 0.5 Gm.

MCNEIL LABORATORIES

Liquid Sulfadiazine: 473 cc. bottles A suspension containing 0.1 Gm. of sulfadiazine in each cubic centimeter.

THE Wm. S. MERRELL COMPANY

Tablets Sulfadiazine: 0.5 Gm.

E. S. MILLER LABORATORIES, INC.

Tablets Sulfadiazine: 0.5 Gm.

PARKE, DAVIS & COMPANY

Tablets Sulfadiazine: 0.5 Gm.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Sulfadiazine: 0.5 Gm.

PITMAN-MOORE COMPANY

Megmoid Sulfadiazine: 360 cc and 3.84 liter bottles A suspension containing 0.1 Gm of sulfadiazine in each cubic centimeter. Preserved with 0.25 per cent benzoic acid.

REXALL DRUG COMPANY

Tablets Sulfadiazine: 0.5 Gm.

WILLIAM H. ROXER, INC.

Tablets Sulfadiazine: 0.5 Gm.

SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Tablets Sulfadiazine: 0.5 Gm

U S patents 2,407,966 and 2,410,793

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Tablets Sulfadiazine: 0.5 Gm

MARVIN R. THOMPSON, INC.

Suspension Sulfadiazine with Sodium Lactate: 473 cc. and 3.78 liter bottles A liquid suspension containing 0.1 Gm. of sulfadiazine and 0.3 Gm of sodium lactate in each cubic centimeter.

U. S. patent 2,460,427.

THE UPJOHN COMPANY

Tablets Sulfadiazine: 0.5 Gm.

THE VALE CHEMICAL COMPANY, INC.

Tablets Sulfadiazine: 0.5 Gm.

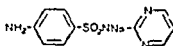
VANFELT & BROWN, INC.

Tablets Sulfadiazine: 0.5 Gm.

WINTHROP-SEARNS, INC.

Tablets Sulfadiazine: 0.5 Gm.

SULFADIAZINE SODIUM—U.S.P.—Soluble Sulfadiazine.—The sodium salt of 2-sulfanilamidopyrimidine—"Sulfadiazine Sodium, dried at 105° for 2 hours, contains not less than 99 per cent of $C_{10}H_9N_4NaO_2S$ " *U.S.P.* The structural formula of sulfadiazine sodium may be represented as follows.



Physical Properties—Sulfadiazine sodium occurs as a white, odorless powder, having a bitter taste. It is very soluble in water. Aqueous solutions may absorb sufficient carbon dioxide to cause precipitation of sulfadiazine. Sulfadiazine sodium is not hygroscopic at 25° if the relative humidity does not exceed 50 per cent.

Actions and Uses—See the general statement on sulfonamides and on pyrimidine derivatives.

Dosage—The usual initial dose for patients who are severely ill with infections which are susceptible to this drug is based on 0.1 Gm. per kilogram of body weight, up to 50 Kg. of body weight. This dose is made up as a 5 per cent solution in sterile distilled water or isotonic solution of sodium chloride. It is injected into a vein. Regardless of the weight of the patient, it is best not to exceed a total initial dosage of 5 Gm. of sulfadiazine sodium.

or sodium sulfadiazine per kilogram of body weight, in a 5 per cent solution in distilled water, administered by the intravenous route at 6-hour to 8-hour intervals.

When solutions of sulfadiazine sodium are being used as the sole therapy, daily determinations of the concentration of the drug in the blood should be made in order to prevent accumulation of inordinately high levels of the drug in the blood. The dosages suggested are applicable to children as well as adults.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

Solution Sodium Sulfadiazine 25%: 10 cc. ampuls. Each cubic centimeter contains 0.25 Gm. of sodium sulfadiazine in distilled water. Preserved with 0.1 per cent sodium thiosulfate.

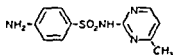
SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Solution Sodium Sulfadiazine 5%: 50 cc ampuls. A solution containing 50 mg of sodium sulfadiazine in each cubic centimeter.

U. S. patents 2,407,966 and 2,410,793

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Powder Sodium Sulfadiazine (*Sterile*): 5 Gm. vials.



Physical Properties.—Sulfamerazine occurs as white or faintly yellowish-white crystals or powder. It has a slightly bitter taste and is odorless or nearly so. It is stable in air but slowly darkens on exposure to light. One gram of sulfamerazine dissolves in about 6,250 cc of water at 20° and in about 3,300 cc at 37°. It is readily soluble in dilute mineral acids and in solutions of potassium, ammonium and sodium hydroxides. It is sparingly soluble in acetone, slightly soluble in alcohol and very slightly soluble in ether and in chloroform.

Actions and Uses.—See the general statement on sulfonamides and on pyrimidine derivatives.

Dosage.—In the treatment of acute pneumococcic, streptococcic and meningococcic infections the maintenance of 10 to 15 mg of sulfamerazine per 100 cc of blood usually will be sufficient. Blood serum concentrations of this magnitude may be attained within 4 hours by the oral administration of 3 or 4 Gm of sulfamerazine as an initial dose, followed by 1 Gm every 8 hours. This schedule should be continued for 72 hours after the temperature, pulse and respiration rates return to normal.

For infants under 6 months of age, the initial dose is 0.5 Gm.

ABBOTT LABORATORIES

Dulcet Tablets Sulfamerazine: 0.3 Gm

U. S. trademark 503,527 (Dulcet)

Tablets Sulfamerazine: 0.5 Gm.

AMERICAN PHARMACEUTICAL COMPANY, INC.

Tablets Sulfamerazine: 0.5 Gm.

BREWER & COMPANY, INC.

Tablets Sulfamerazine: 0.5 Gm.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

Powder Sulfamerazine: 113 and 454 Gm. packages.

Tablets Sulfamerazine: 0.5 Gm.

ELI LILLY & COMPANY

Tablets Sulfamerazine: 0.5 Gm.

S. E. MASSENGILL COMPANY

Tablets Sulfamerazine: 0.5 Gm.

PARKE, DAVIS & COMPANY

Tablets Sulfamerazine: 0.5 Gm.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Sulfamerazine: 0.5 Gm.

SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Powder Sulfamerazine: 113 and 454 Gm. containers.

Tablets Sulfamerazine: 0.5 Gm.

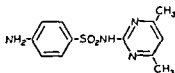
U. S. patent 2,407,966.

THE UPJOHN COMPANY

Tablets Sulfamerazine: 0.5 Gm.

SULFAMETHAZINE-U.S.P.—N¹-(4,6-Dimethyl-2-pyrimidyl) sulfanilamide—"Sulfamethazine contains not less than 99 per cent of C₁₂H₁₄N₄O₂S, dried at 105° for 2 hours." U.S.P.

The structural formula of sulfamethazine may be represented as follows:



Physical Properties.—Sulfamethazine is a white to yellow-white, almost odorless powder with a slightly bitter taste. It may darken on exposure to light and melts between 197 and 200°. It is freely soluble in dilute mineral acids and aqueous solutions of potassium hydroxide and sodium hydroxide, soluble in acetone, slightly soluble in alcohol and very slightly soluble in water.

Actions and Uses.—See the general statement on sulfonamides and on pyrimidine derivatives.

Dosage.—When administered by the oral route to patients suffering from severe infections, the initial dose should be based on 0.1 Gm. per kilogram of body weight but the maximum initial dose of sulfamethazine should not exceed 5 Gm. The maintenance

weight is given daily (approximately 0.5 Gm. per 15 lb.) in three equally divided doses after meals. The drug should be continued for at least a week after all symptoms have disappeared. If no improvement occurs after 10 days of treatment, the drug usually can be considered to have failed in its purpose. For prophylactic use, 0.5 Gm. three times daily after meals is recommended for 24 hours prior to and 48 hours after manipulative or surgical procedures on the genito-urinary tract.

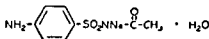
Blood levels should be determined during administration of the drug. In cases of impaired kidney function with above average blood concentration and in any case when the blood level exceeds 12 mg. per cent of free sulfacetamide, the drug should be discontinued and fluids forced.

SCHIERING CORPORATION

Tablets Sulamyd: 0.5 Gm

U S patent 2,411,495 U S trademark 379,386.

SULFACETAMIDE SODIUM-U.S.P.—Sodium Sulamyd (SCHIERING).—The monohydrated sodium salt of N¹-sulfanilylacetylamide—
 lithium contains not less
 U.S.P. The structural



Physical Properties.—Sodium sulfacetamide is a white, odorless, bitter, crystalline powder. One part of sodium sulfacetamide is soluble in 2.5 parts of water. It is sparingly soluble in alcohol and practically insoluble in benzene, chloroform and ether. The pH of a 5 per cent solution is between 8.0 and 9.5. Aqueous solutions of sodium sulfacetamide must be refrigerated and protected from light.

Actions and Uses.—See the general statement on sulfonamides and on sulfacetamide.

The sodium salt is highly soluble at the physiologic pH of 7.4; therefore, it is especially suited, as a solution, for repeated topical application in the local management of ophthalmic infections susceptible to sulfonamide therapy. These include corneal ulcer, blepharitis, blepharoconjunctivitis, dacryocystitis, infections of the eye socket, trachoma and sties.

Local sensitivities frequently noted with other sulfonamides rarely are encountered with sulfacetamide sodium. Care should be exercised, however, to observe the first evidence of any sensitivity, and the drug should be abandoned on the appearance of any undesirable reaction. Do not use with silver preparations.

Dosage.—Sulfacetamide sodium is applied topically to the eye as a 30 per cent solution or as a 10 per cent ointment. The ointment should not be employed in the presence of penetrating wounds of the cornea and ordinarily is reserved for nighttime application as an adjunct to the use of the solution during the day. Pro-

phylactic instillation of one drop of a 30 per cent solution four to six times daily for 2 days is recommended for lesions resulting from corneal abrasions, lacerations, burns or the removal of a foreign body. In acute infections, 1 or 2 drops every 2 hours, or less frequently, is used during the day according to severity; in chronic infections, 1 or 2 drops three or four times daily is considered adequate. At bedtime, application of a small amount of a 10 per cent ointment to the lower lid is recommended.

SCHIERING CORPORATION

Ophthalmic Ointment Sodium Sulamyd 10%: 3.54 Gm. tubes. An ointment containing 0.1 Gm. of sulfacetamide sodium in each gram.

Ophthalmic Solution Sodium Sulamyd 30%: 15 cc bottles. A solution containing 0.3 Gm. of sulfacetamide sodium in each cubic centimeter. Buffered with 0.2 per cent sodium dihydrogen phosphate. Preserved with 0.15 per cent sodium thiosulfate, 0.05 per cent methylparaben and 0.01 per cent propylparaben.

U S patent 2,411,495. U S trademark 379,386.

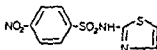
Sulfathiazole Derivatives

The actions and uses of phthalylsulfathiazole and succinylsulfathiazole resemble those of sulfaguanidine. Each has the property of suppressing the growth of bacteria in the large bowel and, hence, may be used preoperatively and postoperatively in surgical procedures on the colon. Each may be used as an adjunct to other methods of treatment in the control of acute and chronic ulcerative colitis.

These derivatives of sulfathiazole are relatively insoluble, and are absorbed poorly from the gastro-intestinal tract; they rarely reach blood concentrations exceeding 2 mg. per 100 cc. of blood. Toxic reactions to therapeutic doses, therefore, are rare. Since both are absorbed poorly, phthalylsulfathiazole and succinylsulfathiazole suppress bacteria in the large bowel by virtue of their high concentration in the lumen of that viscus.

Para-nitrosulfathiazole should be used only for rectal injection as an adjunct in the local treatment of nonspecific ulcerative colitis and proctitis. It probably acts by altering the bacterial flora in the large bowel. It is of more value when the lesions are confined to the sigmoid than when they are diffused through the bowel. Little of the compound is absorbed from the bowel, hence only small amounts pass into the blood.

PARA-NITROSULFATHIAZOLE-N.F.—*N*-sulfazole (BRON).—2-(*p*-Nitrophenyl)sulfonamido) thiazole — "Para-nitrosulfathiazole, dried at 105° for 4 hours, contains not less than 97.5 per cent and not more than 102.5 per cent of $C_9H_7N_3O_4S_2$." *N.F.* The structural formula of para-nitrosulfathiazole may be represented as follows.



Physical Properties.—Para-nitrosulfathiazole is a pale yellow powder. It melts between 255 and 262°. It is slightly soluble in alcohol, very slightly soluble in chloroform, ether and water and practically insoluble in benzene. It is freely soluble in ammonia and sodium hydroxide T.S.

Actions and Uses.—See the general statement on sulfonamides and on sulfathiazole derivatives.

Dosage.—A 10 per cent stabilized suspension of para-nitrosulfathiazole undiluted, or diluted with equal parts of water, is injected rectally by means of a bulb syringe, preferably with the patient in the knee-chest position. The average initial dose is 10 cc. of the 10 per cent suspension, administered after each stool and at bedtime. Larger initial doses of 30 to 60 cc. given four times daily may be required. After improvement is observed, 15 to 30 cc. usually is given once daily at bedtime or less often as needed to maintain freedom from symptoms. Maintenance treatment is advised for 2 to 4 weeks after the mucosa appears normal.

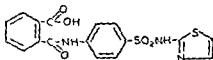
Signs of toxicity from absorption of the drug, which may be due to the presence of large denuded areas of the mucous membrane of the bowel, usually subside promptly upon discontinuance of therapy. Blood or urine levels of the drug may be determined by using a modified application of the method of Bratton and Marshall. (See the general statement on sulfonamide compounds under *Toxicity*.)

GEORGE A. BREON & COMPANY

Suspension Nisulfazole 10%: 237 cc. bottles. A suspension of 0.1 Gm. of para-nitrosulfathiazole in each cubic centimeter. Preserved with oil of peppermint and benzalkonium chloride.

U. S. trademark 418,348

PHTHALYLSULFATHIAZOLE—U.S.P.—Sulfathalidine (SHARP & DOHME).—4'-(2-Thiazolylsulfonyl)phthalanilic acid.—“Phthalylsulfathiazole, dried at 105° for 4 hours, contains not less than 98 per cent of $C_{17}H_{13}N_3O_5S_2$.” U.S.P. The structural formula of phthalylsulfathiazole may be represented as follows:



Physical Properties.—Phthalylsulfathiazole occurs as a white or faintly yellowish-white, crystalline powder. It has a slightly bitter taste and is odorless. It may darken slowly on long exposure to light. Phthalylsulfathiazole is practically insoluble in water and in chloroform. It is slightly soluble in alcohol and very slightly

soluble in ether. It is readily soluble in solutions of alkali hydroxides and their carbonates and in hydrochloric acid.

Actions and Uses.—See the general statement on sulfonamides and on sulfathiazole derivatives

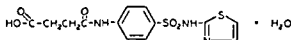
Dosage.—Orally, in tablet form, 0.05 to 0.1 Gm. per kilogram of body weight daily is given in equally divided doses at intervals of 4, 6 or 8 hours, depending on the total dose to be administered. The average daily adult dose is provided by eight to twelve 0.5 Gm tablets and should not exceed 8 Gm. Smaller doses, as indicated by response, may be continued for up to 8 weeks or even longer for the management of ulcerative colitis. As a preliminary adjunct to intestinal surgery, an initial dose of 0.125 Gm per kilogram is given, followed by the same amount daily in divided doses given at equal intervals, comprising three, four or six doses per day, for 3 to 5 days prior to operation.

SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Tablets Sulfathalidine: 0.5 Gm.

U. S. patents 2,324,013, 2,324,015 and 2,576,825 U. S. trademark 408,341

SUCCINYLSULFATHIAZOLE-U.S.P. — Sulfasuxidine (SHARP & DOHME). — *p*-(2-Thiazolylsulfamyl)succinanic acid — "Succinylsulfathiazole, dried at 105° for 4 hours, contains not less than 99 per cent of $C_{13}H_{13}N_3O_3S_2$ " U.S.P. The structural formula of succinylsulfathiazole may be represented as follows:



Physical Properties.—Succinylsulfathiazole occurs as a white or yellowish white crystalline powder. It is odorless and is stable in air, in water, in alcohol, in glycerol, in chloroform and in ether.

Actions and Uses.—See the general statement on sulfonamides and on sulfathiazole derivatives

Dosage.—The initial preoperative dose is 0.25 Gm per kilogram of body weight by mouth, followed by a maintenance dose of 0.25 Gm per kilogram daily in six equal portions at 4-hour intervals. The postoperative dose is 0.25 Gm per kilogram daily for 1 or 2 weeks, depending on the postoperative condition. Postoperative administration should be begun as soon as the patient can take an ounce of water without undue nausea.

SHARP & DOHME, DIVISION OF MERCK & CO., INC.

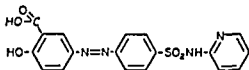
Powder Sulfasuxidine: 113 and 454 Gm. glass jars

Tablets Sulfasuxidine 0.5 Gm

U. S. patents 2,324,013, 2,324,014 and 2,576,825 U. S. trademark 394,111.

Other Sulfonamide Compounds

SALICYLAZOSULFAPYRIDINE.—Azulfidine (PIRABACIA).—5-[p-(2-Pyridylsulfamyl)phenylazo]salicylic acid.—The structural formula of salicylazosulfapyridine may be represented as follows:



Physical Properties.—Salicylazosulfapyridine is a brownish yellow, odorless powder, which melts between 220 and 240° (with decomposition). It is slightly soluble in alcohol and practically insoluble in benzene, chloroform, ether and water.

Actions and Uses.—Salicylazosulfapyridine shares the actions of related sulfonamide compounds, including the potential toxic effects of sulfapyridine. Because the drug has been found to have a special affinity for connective tissue, it is proposed for use in chronic ulcerative colitis. Available clinical evidence confirms its usefulness only for this purpose and does not justify conclusions that its selective retention in connective tissue is of therapeutic significance or that it is clinically superior to other sulfonamide compounds in this condition.

When administered in this condition, the drug is excreted through the urine. It produces an orange-yellow color when the urine is alkaline and no color when the urine is acid.

Dosage.—Salicylazosulfapyridine is administered orally only. The average dose for adults is 1 Gm four to six times daily with no interval of more than 8 hours between doses. Larger doses may be employed in severe cases. For children over 7 years of age, the average dose is 0.5 to 1 Gm three to six times daily; children 5 to 7 years of age, 0.25 to 0.5 Gm three to six times daily.

Usual doses produce a blood concentration of sulfapyridine that seldom exceeds 1 to 2 mg per 100 cc, a level considerably lower than that produced with the formerly recognized use of sulfapyridine as such. If slight nausea occurs, the dosage should be reduced by one-half. If nausea is severe, treatment should be discontinued for 2 days and then resumed at one-half the original dosage for 3 days before returning to full dosage. Results of therapy should be followed by proctoscopy. Treatment should be continued until such observations reveal satisfactory response even when diarrhea has stopped. After proctoscopic examination reveals improvement, the adult dosage should be reduced to 0.5 Gm. three times daily.

Because of the unusual toxicity of sulfapyridine as compared with other sulfonamides, patients should be observed especially for toxic manifestations characteristic of this group of drugs. If leukopenia or severe drug fever and exanthema appear, therapy should

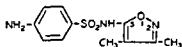
be discontinued immediately. Periodic blood counts and careful observation are essential.

PHARMACIA LABORATORIES, INC.

Tablets Azulfidine: 0.5 Gm.

U. S. patent 2,396,145 U. S. trademark 571,960

SULFISOXAZOLE-U.S.P.—Gantrisin (HOFFMANN-LA ROCHE).—*N*¹-3,4-Dimethyl-5-isoxazolylsulfanilamide — "Sulfisoxazole contains not less than 99 per cent of $C_{11}H_{13}N_3O_3S$, dried at 105° for 2 hours" *U.S.P.* The structural formula of sulfisoxazole may be represented as follows:



Physical Properties.—Sulfisoxazole is a white, odorless, slightly bitter, crystalline powder. It melts between 192 and 195°. It is freely soluble in diluted hydrochloric acid and soluble in alcohol.

Actions and Uses.—Sulfisoxazole shares the actions and uses of other sulfonamide derivatives (See the general statement on sulfonamides.) Certain patients ill with urinary tract infections produced by organisms of the *Proteus* group respond satisfactorily to treatment with sulfisoxazole. It may vary in its effectiveness against different strains of sulfonamide-sensitive micro-organisms. Because of its relatively high solubility in body fluids, the drug is less likely to produce crystalluria and renal blocking than less soluble sulfonamide derivatives employed singly, otherwise it has the same potentiality for toxic reactions.

Dosage.—The initial oral dose for adults is 4 to 6 Gm., followed by 1 to 2 Gm. every 4 hours until temperature has been normal for at least 48 hours.

For children, the dose is 100 mg. per kilogram of body weight may be given in 4 to 6 divided doses at 4-hour intervals, until temperature is normal for 48 hours.

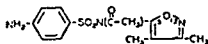
HOFFMANN-LA ROCHE, INC.

Powder Gantrisin. 113.4 and 454 Gm. bottles.

Tablets Gantrisin: 0.5 Gm.

U. S. patent 2,430,694 U. S. trademark 515,767

ACETYL SULFISOXAZOLE.—Gantrisin Acetyl (HOFFMANN-LA ROCHE).—*N*¹-(Acetyl-3,4-dimethyl-5-isoxazolyl) sulfanilamide — The structural formula of acetyl sulfisoxazole may be represented as follows:



Physical Properties.—Acetyl sulfisoxazole is a white to slightly off-white, crystalline solid, with a slight characteristic odor and with a melting point between 192 and 195°. It is practically insoluble

in the

in alcohol

Acetic

uses of

is tasteless and, therefore, suitable for oral administration, especially in liquid preparations of the drug. There is evidence to support the assumption that the acetyl compound is split in the intestinal tract and absorbed as sulfisoxazole; hence, the absorption, the excretion, and the solubility of acetyl sulfisoxazole in body fluids are considered to be the same as for the parent drug. It has been found to have about the same toxicity as sulfisoxazole and should be employed with the usual precautions for sulfonamide compounds.

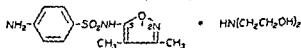
Dosage.—Acetyl sulfisoxazole is administered orally. The dosage is expressed in terms of sulfisoxazole and calculated on the basis of 0.5 Gm per 9 Kg (20 lb) of body weight as the initial dose, followed by one-half the initial dose every 4 hours. In severe infections, these doses may be doubled

HOFFMANN-LA ROCHE, INC.

Suspension Gantrisin Acetyl (Pediatric): 118.3 and 473 cc. bottles. A flavored suspension containing 0.1 Gm. of sulfisoxazole as acetyl sulfisoxazole in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben

Syrup Gantrisin Acetyl: 118.3 and 473 cc bottles. A flavored syrup containing 0.1 Gm. of sulfisoxazole as acetyl sulfisoxazole in each cubic centimeter. Preserved with 0.3 per cent benzoic acid

made by adding enough diethanolamine to a solution of sulfisoxazole to bring the pH to about 7.5. The structural formula of sulfisoxazole diethanolamine may be represented as follows:



Actions and Uses.—Sulfisoxazole diethanolamine is used as a salt of sulfisoxazole to make the drug more soluble at the physiologic pH range of 6.0 to 7.5. Diethanolamine reacts with the sulfisoxazole to form a soluble salt. The diethanolamine salt, therefore, is used in solution for systemic administration of the drug by slow intravenous, intramuscular or subcutaneous injection when suffi-

tion. (See the monograph on sulfisoxazole and the general statement on sulfonamides.)

Dosage.—A solution of 40 per cent sulfisoxazole in the form of the diethanolamine salt may be used for slow intravenous or intramuscular injection. No more than 5 cc. intramuscularly should be injected at any one site. For intravenous administration, the sulfisoxazole must be diluted with sterile water to 5 per cent or less. The parent drug, sulfisoxazole (see the monograph on sulfisoxazole). Intravenous, intramuscular or subcutaneous injection should not replace oral administration except when the drug cannot be administered adequately by that route.

For ophthalmic use, a solution or ointment of 4 per cent sulfisoxazole in the form of the diethanolamine salt may be used.

Ophthalmic preparations of sulfisoxazole diethanolamine should be used cautiously, especially in patients who previously have exhibited sensitivity to sulfonamides. If undesirable reactions occur during such use, the drug should be discontinued immediately. Silver preparations must not be used concurrently for ophthalmic application.

HOFFMANN-LA ROCHE, INC.

Ophthalmic Ointment Gantrisin Diethanolamine 4%: 3.54 Gm. tubes. An ointment containing 40 mg. of sulfisoxazole in the form of the diethanolamine salt in each gram. Preserved with 0.002 per cent phenylmercuric nitrate.

Ophthalmic Solution Gantrisin Diethanolamine 4%: 30 cc. dropper bottles. A solution containing 40 mg. of sulfisoxazole as the diethanolamine salt in each cubic centimeter. Preserved with 0.001 per cent phenylmercuric nitrate.

Solution Gantrisin Diethanolamine. 5 and 10 cc. ampuls. A solution containing 0.4 Gm. of sulfisoxazole as the diethanolamine salt in each cubic centimeter.

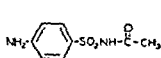
Sulfonamide Mixtures

Mixtures of the three pyrimidine derivatives

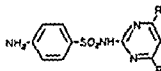
...decreased. Danger of damage to the kidneys during the use of these agents is diminished.

because each sulfonamide is present in less concentration than when used alone and renal excretion of the sulfonamides apparently is individual rather than additive. The therapeutic efficacy of the mixtures, however, is that of the sum of the components.

SULFACETAMIDE, SULFADIAZINE, AND SULFAMERAZINE-N.F.
 —Sulfacetamide (TUTAG).—Cetazine (BOWMAN BROS.).—Dorsulfas (SERRIT-DORSEY).—Incorporsol (BLUE LINE).—Tricombisol (SCHERING).—"Sulfacetamide, Sulfadiazine, and Sulfamerazine Suspension [and Tablets] contain(s) not less than 90 per cent and not more than 110 per cent of the labeled amounts of - - -"
 $(C_8H_{10}N_2O_3S)$, sulfadiazine $(C_{10}H_8N_4O_2S)$,
 $(C_{11}H_{12}N_4O_2S)$ "N.F. They may be represented as follo



Sulfacetamide

Sulfadiazine, $R = R' = H$
Sulfamerazine, $R = H, R' = CH_3$

Actions and Uses.—See the general statement on sulfonamide mixtures. For specific indications and contraindications to the use of the drugs, see the general statement on sulfonamides.

Dosage.—The mixture of sulfacetamide, sulfadiazine and sulfamerazine is administered orally. In adults, 4 Gm. total sulfonamides is given as the initial dose, followed by 1 Gm. every 4 hours until signs of infection have been absent for at least 48 hours. Then 3 to 4 Gm. in divided doses is given daily for an additional 2 to 3 days depending upon the type and severity of infection. In children, the average daily dose should be calculated on the basis of 0.1 Gm. per kilogram of body weight, one-third of this amount is given as the initial dose, followed by one-sixth of the total daily dose every 4 hours. This amount should be continued as a maintenance dose until signs of infection have subsided for at least 36 hours. Thereafter, two-thirds to one-half of the original maintenance dose may be given for an additional 2 to 3 days, again depending upon the type and severity of the infection. The blood concentration of sulfonamides should be maintained between 5 and 15 mg. per 100 cc.

THE BLUE LINE CHEMICAL COMPANY

Suspension Incorporsol. 60 and 473 cc. bottles. A suspension containing 44 mg. each of sulfacetamide, sulfadiazine and sulfamerazine in each cubic centimeter. Preserved with 0.05 per cent methylparaben and 0.01 per cent propylparaben.

Tablets Incorporsol. 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfacetamide, sulfadiazine and sulfamerazine.

THE BOWMAN BROS DRUG COMPANY

Tablets Cetazine. 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfacetamide, sulfadiazine and sulfamerazine.

Hexad Tablets Cetazine 0.25 Gm. Each tablet contains 83 mg. each of sulfacetamide, sulfadiazine and sulfamerazine

SCHERING CORPORATION

Liquid Tricombisul: 473 cc. bottles A suspension containing 42 mg each of sulfacetamide, sulfadiazine and sulfamerazine in each cubic centimeter. Preserved with 0.05 per cent methylparaben and 0.01 per cent propylparaben

Tablets Tricombisul: 0.5 Gm. Each tablet contains 0.166 Gm. each of sulfacetamide, sulfadiazine and sulfamerazine.

U. S. trademark 538,898.

SMITH-DORSEY, DIVISION OF THE WANDER COMPANY

Suspension Dorsulfas: 473 cc. bottles A suspension containing 33 mg each of sulfacetamide, sulfadiazine and sulfamerazine in each cubic centimeter.

Tablets Dorsulfas: 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfacetamide, sulfadiazine and sulfamerazine.

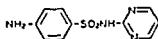
U. S. trademark 563,121

S. J. TUTAG & COMPANY

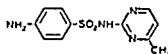
Suspension Buffonamide with Sodium Citrate: 473 cc. and 3.78 liter bottles A suspension containing 33 mg each of sulfacetamide, sulfadiazine and sulfamerazine, and 0.1 Gm. of sodium citrate in each cubic centimeter Preserved with 0.75 per cent methylparaben and 0.25 per cent propylparaben

Wax-sulfin
10TT)
4-Mill
duplex
and

Sulfamerazine [Tablets] contain not less than 90 per cent and not more than 110 per cent of the labeled amounts of sulfadiazine ($C_{10}H_{10}N_4O_2S$) and sulfamerazine ($C_{11}H_{12}N_4O_2S$). *N.F.* The structural formulas of the sulfonamides may be represented as follows



Sulfadiazine



Sulfamerazine

Actions and Uses.—See the general statement on sulfonamides and on sulfonamide mixtures.

Dosage.—In the treatment of acute pneumococcic, streptococcic and meningococcic infections the maintenance of a blood concentration of 10 to 15 mg. of total sulfonamides per 100 cc. is usually sufficient. Blood serum concentrations of this magnitude may be attained within 4 hours by the oral administration of 3 or 4 Gm. of total sulfonamides as an initial dose, followed by 1 Gm. every 6 hours. This dosage should be continued for 72 hours after the temperature and pulse and respiration rates return to normal. In severe infections it may be desirable to increase the dosage; however, concentrations in excess of 12 mg. of the combined drugs per 100 cc. of blood rarely are needed.

For children the initial dose of 65 to 100 mg. total sulfonamides per kilogram of body weight is followed by one-quarter the initial dose every 6 hours. Dosage should be adjusted to meet the requirements of each case.

ABBOTT LABORATORIES

Dulcet Tablets Duozone: 0.3 Gm. Each tablet contains 0.15 Gm. each of sulfadiazine and sulfamerazine.

0.15 Gm. Each tablet contains 75 mg. each of sulfadiazine and sulfamerazine.

U. S. trademark 500,527 (Dulcet).

Suspension Duozone with Sodium Citrate: 473 cc. and 3.78 liter bottles. A suspension containing 30 mg. each of sulfadiazine and sulfamerazine and 0.3 Gm. of sodium citrate in each cubic centimeter.

Tablets Duozone: 0.5 Gm. Each tablet contains 0.25 Gm. each of sulfadiazine and sulfamerazine.

U. S. trademark 546,525.

ARLINGTON-FUNK LABORATORIES, DIVISION OF U. S. VITAMIN CORPORATION

Syrup Duo-Sulfanyl with Sodium Citrate: 118.3 and 473 cc. and 3.78 liter bottles. A suspension containing 50 mg. each of sulfadiazine and sulfamerazine and 0.1 Gm. of sodium citrate in each cubic centimeter.

THE BOWMAN BROS. DRUG COMPANY

Tablets Merdisul: 0.5 Gm. Each tablet contains 0.25 Gm. each of sulfadiazine and sulfamerazine.

Hexett Tablets Merdisul: 0.13 Gm. Each tablet contains 64.8 mg. each of sulfadiazine and sulfamerazine.

ELI LILLY & COMPANY

Savorets (Flavored Tablets) Sulfonamides Duplex: Each tablet contains 0.125 Gm. each of sulfadiazine and sulfamerazine.

Suspension Sulfonamides Duplex: 473 cc. bottles. A suspension containing 50 mg. each of sulfadiazine and sulfamerazine in each cubic centimeter.

Tablets Sulfonamides Duplex: Each tablet contains 0.25 Gm. each of sulfadiazine and sulfamerazine.

McNEIL LABORATORIES, INC.

Liquoid Mor-Diazine: 120 and 473 cc. bottles. A suspension containing 50 mg. each of sulfamerazine and sulfadiazine in each cubic centimeter.

U. S. trademark 553,726

E. S. MILLER LABORATORIES, INC.

Tablets Sul-Di-Mill with Sodium Bicarbonate: Each tablet contains 0.22 Gm. each of sulfadiazine and sulfamerazine and 0.3 Gm. sodium bicarbonate.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Sulmeradine: 0.5 Gm. Each tablet contains 0.25 Gm. each of sulfadiazine and sulfamerazine.

PITMAN-MOORE COMPANY

Magmaoid Sulfadimer with Sodium Lactate: 354.9 cc. and 3.78 liter bottles. A suspension containing 50 mg. each of sulfadiazine and sulfamerazine and 0.1 Gm. of sodium lactate in each cubic centimeter.

WILLIAM R. RORER, INC.

Suspension Disulfyn: 60 and 473 cc. bottles. A suspension containing 50 mg. each of sulfadiazine and sulfamerazine in each cubic centimeter.

Tablets Disulfyn: Each tablet contains 0.25 Gm. each of sulfadiazine and sulfamerazine.

THE VALE CHEMICAL COMPANY, INC.

Tablets Diamerzine: 0.5 Gm. Each tablet contains 0.25 Gm. each of sulfadiazine and sulfamerazine.

VELTEX COMPANY

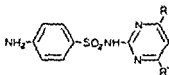
Suspension Bisulfon with Sodium Lactate: 480 cc. and 3.84 liter bottles. A suspension containing 50 mg. each of sulfadiazine and sulfamerazine and 0.1 Gm. sodium lactate in each cubic centimeter.

THE WARREN-TEED PRODUCTS COMPANY

Suspension Bi-Sulfazine: 473 cc. and 3.78 liter bottles. A suspension containing 50 mg. each of sulfadiazine and sulfamerazine in each cubic centimeter.

—Sulfatryl (WALSH) —Tersulfonyl (SULLIVAN) —Tersulfate (BOYLE) —
Trifonamide (VANPelt & Brown) —Trionamide (FLINT, EATON) —
Tripazine (EATON) —Tri-Sulfameth (ARLINGTON-FUNK) —Trisulfa-

zine (CENTRAL).—Truozine (ABBOTT).—"Oral Trisulfapyrimidines Suspension [and Tablets] contain(s) not less than 93 per cent and not more than 108 per cent of the labeled amount of total sulfapyrimidines, consisting of sulfadiazine ($C_{10}H_{10}N_4O_2S$), sulfamerazine ($C_{11}H_{12}N_4O_2S$), and sulfamethazine ($C_{12}H_{14}N_4O_2S$). The amount of each of the three sulfapyrimidines is not less than 30 per cent and not more than 37 per cent of the labeled amount of total sulfapyrimidines." *U.S.P.* The structural formula of the sulfonamides may be represented as follows:



SULFADIAZINE, $R = R' = H$

SULFAMERAZINE, $R = H, R' = CH_3$

SULFAMETHAZINE, $R = R' = CH_3$

Actions and Uses—See the general statement on sulfonamides and on sulfonamide mixtures.

Dosage.—In the treatment of acute pneumococcal, streptococcal and meningococcal infections the maintenance of a blood concentration of total sulfonamide drugs of 10 to 15 mg. per 100 cc usually will be sufficient. Blood serum concentrations of this magnitude may be attained within 4 hours by the oral administration of 3 or 4 Gm. of the triple sulfonamide mixture as an initial dose, followed by 1 Gm. every 6 hours. This dosage should be continued for 72 hours after the temperature and pulse and respiration rates return to normal. In severe infections, it may be desirable to increase the dosage. However, blood concentrations of the combined drugs in excess of 12 mg. per 100 cc. rarely are needed.

For children an initial dose of 65 to 100 mg. of total sulfonamide drugs per kilogram of body weight is followed by one-quarter the initial dose every 6 hours. Dosage should be adjusted to meet the requirements of the particular case.

Sulfonamide mixtures are suited only for oral administration.

ABBOTT LABORATORIES

Suspension Truozine with Sodium Citrate (Flavored): 473 cc bottles. A suspension containing 20 mg. each of sulfadiazine, sulfamerazine and sulfamethazine and 0.3 Gm. of sodium citrate in each cubic centimeter.

Dulcet Tablets Truozine: Each tablet contains 0.1 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

U. S. trademark 500,527 (Dulcet).

Tablets Truozine: Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

U. S. trademark 565,944

AMERICAN PHARMACEUTICAL COMPANY

Tablets Sulfa-Ter: 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine

ARLINGTON-FUNK LABORATORIES, DIVISION OF U S VITAMIN CORPORATION

Syrup Tri-Sulfameth: 118.3 and 473 cc. and 3.78 liter bottles. A syrup containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine and 0.1 Gm. of sodium citrate in each cubic centimeter.

Tablets Tri-Sulfameth: 0.5 Gm. Each tablet contains 0.165 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

BOYLE & COMPANY

Tablets Tersulfas: 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine

THE CENTRAL PHARMACAL COMPANY

Palatabs Trisulfazine: 0.25 Gm. Each tablet contains 83 mg. each of sulfadiazine, sulfamerazine and sulfamethazine

Suspension Trisulfazine with Sodium Lactate: 60 and 473 cc. and 3.78 liter bottles. A stable suspension containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine and 0.1 Gm. of sodium lactate in each cubic centimeter. Preserved with methylparaben and propylparaben

Tablets Trisulfazine: 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine

THE COLUMBUS PHARMACAL CO

Pediatabs Palatrine: 0.125 Gm. Each tablet contains 42 mg. each of sulfadiazine, sulfamerazine and sulfamethazine

EATON LABORATORIES

Tablets Tripazine: 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine

FLINT, EATON & COMPANY

Suspension Trionamide with Sodium Citrate: 60 and 473 cc. and 3.78 liter bottles. A suspension containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine and 66 mg. of sodium citrate in each cubic centimeter.

KREIERS-URBAN COMPANY

Tablets Multazine: 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

LLOYD & DOWNEY COMPANY, INC

Tablets Sulfaloid: 0.25 Gm. Each tablet contains 83 mg. each of sulfadiazine, sulfamerazine and sulfamethazine.

0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

McNEIL LABORATORIES, INC.

Liquid Metha-Merdiazine: 120 and 473 cc. bottles. A homogenized dispersion containing 33 mg each of sulfadiazine, sulfamerazine and sulfamethazine in each cubic centimeter.

Tablets Metha-Merdiazine: 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

U. S. trademark 533,769

PREMO PHARMACEUTICAL LABORATORIES, INC.

Suspension Meth-Dia-Mer-Sulfonamides: 473 cc. bottles. A suspension containing 33 mg each of sulfadiazine, sulfamerazine and sulfamethazine in each cubic centimeter.

Tablets Meth-Dia-Mer-Sulfonamides: 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

RAYMER PHARMACAL COMPANY

Suspension Ray-Tri-Mides: 473 cc. and 3.78 liter bottles. A suspension containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine in each cubic centimeter.

Tablets Ray-Tri-Mides: 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

REXALL DRUG COMPANY

Tablets Sulfa-Trio: 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Suspension Terfonyl: 473 cc. bottles. A suspension containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine in each cubic centimeter. Preserved with 0.05 per cent each of methylparaben and propylparaben.

Tablets Terfonyl: 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

U. S. trademark 536,646

MARVIN R. THOMPSON, INC.

Suspension Sulfa-tri-azine with Sodium Lactate: 473 cc. and 3.78 liter bottles. A suspension containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine and 0.3 Gm. of sodium lactate in each cubic centimeter.

U. S. patent 2,460,437.

VANPELT & BROWN, INC.

Suspension Trifonamide: 360 cc. bottles. A suspension containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine in each cubic centimeter.

Tablets Trifonamide: 0.5 Gm Each tablet contains 0.166 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.
U S trademark 505,633

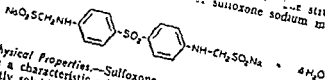
HENRY K. WATPOLE & COMPANY, INC.

Granules Sulfatryl for Suspension with Sodium Citrate: Flavored granules which when mixed with 60 cc. of water yield a suspension containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine and 0.1 Gm of sodium citrate in each cubic centimeter.

Sulfone Compounds

SULFOXONE SODIUM.—U.S.P.—Disodium

(Absorb.)—Sulfononon, disodium tetrahydrate.—Sulfononon, disodium tetrahydrate. It may be represented as a structural formula for the active compound, sulfoxone sodium may be represented as follows.



Physical Properties.—Sulfoxone sodium is a pale yellow powder with a characteristic odor. It is very soluble in water and very slightly soluble in alcohol. The aqueous solution is clear and pale yellow.

Actions and Uses.—Sulfoxone sodium is indicated in the treatment of leprosy. Lesions usually do not progress under therapy, although not all respond favorably. The earliest and most frequent signs of response are healing of mucous membrane lesions followed by improvement in skin lesions. The latter consists of fading of macules and plaques, softening and flattening of nodules and decrease in diffuse infiltration. Nodules diminish in size and in most instances resorption is complete. Sometimes there is necrosis of nodules followed by ulceration and rapid healing.

The commonest toxic effect of the drug is a transient normocytic anemia, but withdrawal is not indicated unless the anemia becomes severe. Usually, recovery from the anemia takes place between the third and sixth week of therapy. Methemoglobinemia, which occurs in about half the patients, is not an indication for withdrawal of the drug unless anoxemia is acute. Other toxic effects are nausea, hematuria, drug rashes and leukopenia.

Dosage.—Treatment is started with small doses. The usual initial dose for adults is 0.3 Gm. daily. If no symptoms of intolerance appear during the first week of treatment, the dose may be increased to 0.6 Gm. daily. This dosage is continued for 2 or 3 weeks. If no symptoms of intolerance develop, the dose may be increased to 0.9 Gm. daily and continued at this rate for 6 months or more if no severe side effects develop. At least 6 months are required to evaluate therapeutic effect. Rest periods of 2 weeks every 2 months are advisable.

For children 6 to 12 years old the initial dose is 0.15 Gm. daily, increasing at monthly intervals to 0.6 Gm. if there are no contraindications. For children 4 to 6 years old the maximum daily dose may be 0.45 Gm. Information concerning treatment of younger children is not available.

ABBOTT LABORATORIES

Enterab Tablets Dione Sodium: 0.33 Gm.

U. S. patent 2,256,575 and Licensed under U. S. patent 2,234,981, U. S. trademarks 407,420 and 353,674 (Enterab).

ANTIBIOTICS

The group of substances referred to as antibiotics are chemically dissimilar and, originally, were produced in cultures during the active growth phase of certain bacteria or molds. They have one property in common: they produce bacteriostatic or bactericidal effects on susceptible micro-organisms.

Some are synthesized by chemical methods, and the latter now is produced commercially by a synthetic process. The pharmacologic properties of the various antibiotics must be considered separately because of the diversity among these substances.

Bacterial Resistance.—The selection of the proper and most effective antibiotic for the systemic treatment of particular infections is becoming more difficult as potent antibiotics with similar therapeutic powers appear. However, one important factor is the increasing resistance of some species of pathogenic micro-organisms to the antibacterial effects of certain antibiotics.

One of the most common examples of this phenomenon is the resistance of strains of *Staph. aureus* to penicillin. This phenomenon has shown that these strains of staphylococci are resistant to the antibacterial effects of certain antibiotics.

ingococci or gonococci have developed increased resistance to the antibacterial effects of penicillin.

With streptomycin and dihydrostreptomycin, the situation is even worse. One competent investigator has reported that, of the pathogenic strains of the following organisms that were isolated from diseased tissue in 1949, 33 per cent of the strains of *E. coli*, 45 per cent of the strains of *A. aerogenes*, 70 per cent of the strains of *Proteus*, 77 per cent of the strains of *P. aeruginosa*, 33 per cent of the strains of nonhemolytic streptococci and 77 per cent of the strains of *Str. fecalis* were resistant, and often highly resistant, to the antibacterial effects of streptomycin. Another serious discovery has been made. Infants exposed to persons with infectious streptomycin-resistant tuberculosis, have developed tuberculous meningitis primarily resistant to streptomycin. Resistance to streptomycin develops easily by mutation, or the selection out of resistant strains, of the micro-organism and, in the majority of instances of nontuberculous infections, develops within the first week of therapy.

Indications.—Penicillin G is still the antibiotic of choice for the systemic treatment of infections produced by beta hemolytic streptococci (Lancefield's Group A), pneumococci, meningococci, gonococci, the spirochetes, *Cl. welchii* and actinomycosis. Chlorotetracycline and oxytetracycline also are effective in these infections, except that oxytetracycline is not effective in actinomycosis. In infections produced by *Staph. aureus*, *Str. fecalis*, *L. monocytogenes*, the Bacteroides and *Lept. icterohemorrhagica*, chlorotetracycline and oxytetracycline are the most effective antibiotics. In tuberculosis, streptomycin and aminosalicylic acid should be used.

Chlorotetracycline, chloramphenicol and oxytetracycline are equally effective in brucellosis, tularemia, bacillary infections caused by *E. coli*, *A. aerogenes*, *Kl. pneumoniae*, the Shigella group of infections, chancroid, granuloma inguinale, bacillary dysentery and rickettsial diseases.

Clinical reports seem to indicate that chlorotetracycline, chloramphenicol and oxytetracycline are beneficial therapeutic agents in the treatment of whooping cough.

All are effective, but chlorotetracycline particularly so, in psittacosis, lymphogranuloma venereum and primary atypical pneumonia. While all three are effective in certain stages of syphilis, their value, relative to penicillin, awaits further study.

Only chloramphenicol is really effective in typhoid fever. Chloramphenicol and chlorotetracycline, used with a pyrimidine derivative of sulfanilamide, are of value in meningitis caused by *Hemophilus influenzae*. Chlorotetracycline and oxytetracycline are effective in acute amebic dysentery. Chlorotetracycline is the antibiotic of choice for local treatment of vaginitis produced by *Trichomonas vaginalis*.

Chlorotetracycline, chloramphenicol and oxytetracycline may be used for the suppression of bacterial growth in the stool as a pre-operative and postoperative prophylactic measure in surgery of the large bowel. Chlorotetracycline has proved very effective as a prophylactic in puerperal sepsis. Penicillin is valuable in the prophylaxis of gonorrhea, syphilis, acute rheumatic fever and sepsis following the extraction of teeth or after "clean" surgery. Streptomycin

is effective in the therapy of tissue infections produced by (non-resistant strains of) *Proteus* or *Pseudomonas aeruginosa* organisms. However, in infections caused by *Ps. aeruginosa*, polymyxin B is the antibiotic of choice. None of the antibiotics is of proved value in paratyphoid fevers and other *Salmonella* infections. There is little or no evidence that any of the antibiotics is effective in the treatment of the common cold, influenza, measles, mumps, acute

Toxicity.—All currently accepted antibiotics produce toxic reactions in some people. Allergic reactions, manifested by various types of skin eruptions or lesions, with or without painful swollen joints, are common when penicillin, streptomycin or dihydrostreptomycin is administered to a sensitive patient. Persons allergic to procaine react similarly to procaine penicillin. Similar types of skin reactions have been rare during therapy with chlortetracycline, chloramphenicol or oxytetracycline. Contact dermatitis may be produced by antibiotics, particularly streptomycin and penicillin. Asthma has developed as a toxic reaction to penicillin by inhalation and lesions of the mucous membranes have followed penicillin (by mouth), chlortetracycline, chloramphenicol and oxytetracycline. Anaphylac-

biotics has not been reported. Changes in the peripheral blood or the blood-forming organs have been reported only during the use of chloramphenicol. Mild hemolytic anemias, granulocytopenia, and fatal cases of aplastic anemia have

been reported with chloramphenicol. Lesions of the blood-forming organs have been attributed to penicillin therapy. Vertigo, tinnitus, disturbances in equilibrium and deafness, due to eighth nerve injury, are well known as complications in therapy with streptomycin or dihydrostreptomycin. Although partial recovery of eighth nerve function may occur, numerous examples of permanent vestibular dysfunction and deafness have been reported, especially following the use of dihydrostreptomycin. Nausea and vomiting may be produced by chlortetracycline, chloramphenicol or oxytetracycline, the incidence incre-

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velop. Loose stools or frank diarrhea may also result from the use of antibiotics. Mild hemolytic anemias, granulocytopenia, and fatal cases of aplastic anemia have been reported with chloramphenicol, streptomycin, or all

ycline

have powerful suppressive effects on the normal bacterial flora of the mouth, vagina and large intestine, and abnormal flora elsewhere, superimposed infections (or infestations) with yeastlike organisms may occur. Hence, thrush and moniliasis of the skin, especially in the peri-anal region, and of the mucous surfaces of the vagina and lower rectum are not uncommon. Moniliasis of the lungs has followed the prolonged use of chlortetracycline, chloramphenicol or oxytetracycline for the treatment of bronchiectasis. All lesions of the skin or mucous membranes that occur in the course of therapy with chlortetracycline, chloramphenicol or oxy-

possibility must be considered when lesions of mucous membranes occur.

For tyrothricin see the chapter on local anti-infectives.

Bacitracin

BACITRACIN-U.S.P.—"Bacitracin is an antibacterial substance produced by the growth of a gram-positive, spore-forming organism belonging to . . .

It has a potency that when intended

50 U.S.P. Units per mg and when intended for the manufacture of ointments, tablets and troches, it may have a potency of not less than 30 U.S.P. Units per mg. Bacitracin conforms to the regulations of the Federal Food and Drug Administration concerning certification of antibiotic drugs." U.S.P.

Physical Properties.—Bacitracin is a white to pale buff hygroscopic powder and is odorless or has a slight odor. Its solutions deteriorate rapidly at room temperature. It is precipitated from solution and is inactivated by salts of many of the heavy metals. It is freely soluble in water, soluble in alcohol, in methanol and in glacial acetic acid, although the solution in the organic solvents usually shows some insoluble residue. It is insoluble in acetone, in chloroform and in ether.

Actions and Uses.—Bacitracin is a bactericidal antibiotic effective against a wide variety of gram-positive organisms, including hemolytic and nonhemolytic streptococci, staphylococci and pneumococci, anaerobic cocci and clostridia of the gas gangrene group, corynebacteria, the . . .

Actinomyces visus, a gonococci and meningococci and aerobic gram-negative

ment of infections caused by susceptible organisms and is often successful when such infections have failed to respond to penicillin and other antibiotics. Its speed of bactericidal action is in direct proportion to its concentration. Bacitracin is eliminated from the body slowly, traces are present in the blood 6 to 8 hours after

intramuscular injection. Patients are seldom, if ever, primarily sensitive to bacitracin, nor do they develop sensitivity to it following repeated courses of the antibiotic. Bacteria are very slow in developing resistance to bacitracin.

Bacitracin may be used by intramuscular injection in the treatment of systemic infections caused by organisms susceptible to the antibiotic and by local injection into circumscribed areas of infection, such as furuncles, carbuncles or abscesses, often obviating surgery. Either alone or in conjunction with intramuscular therapy, it has been used successfully and safely by the intrathecal, intraventricular, intracisternal or intracerebral injection in the treatment of susceptible neurosurgical infections, including osteomyelitis of the skull, septic coccal meningitis, brain abscess and postoperative infections. Bacitracin also is employed locally by topical application in water-soluble or petrolatum ointment bases or in aqueous or saline solutions in the treatment of infections of the skin, eye, nose and throat or in surgical infections of the soft parts and bone, as well as in the prophylactic and active treatment of infected burns. It has been used by inhalation for susceptible respiratory tract infections. Because it is not absorbed from the gastro-intestinal tract, oral use of large quantities does not result in detectable blood levels. Its oral use for intestinal amebic infection has been successful.

Bacitracin is a polypeptide, and the intramuscular injection of large doses may produce renal tubular swelling. With the smaller doses, traces of albuminuria may be observed on the second or third day and usually fade away by the fourth day. It is noted that the kidneys excrete bacitracin in the urine as albuminuria, cellular casts and granular casts. With larger doses, these casts may be numerous.

It is certain that fluid intake is adequate—for adults, 2,500 cc. a day and for children a corresponding amount. Other side effects include loss of appetite and, occasionally, nausea and vomiting. Urticaria is extremely rare. There may be some painful induration at the site of injection; therefore, to minimize or obviate any untoward side reactions when bacitracin is administered intramuscularly, care should be exercised not to exceed the maximum advocated dosage and to assure adequate intake of fluid (2,500 cc. a day).

Before intramuscular therapy is initiated, if the facilities are available, the urine should be examined for albumin, casts and cellular elements, blood determinations should be made for either urea nitrogen or nonprotein nitrogen. During the period of treatment, patients should be checked routinely for evidences of renal damage; the urine should be examined for albumin and cellular pathology every other day, and the blood checked weekly for evidence of retained nitrogen. However, the results of these examinations are not likely to be alarming if intake of fluid is adequate.

The fluid intake and urinary output should be measured carefully every day. This is the most important factor in respect to kidney

function. If output remains above 1,000 cc., there need be little fear of toxicity. If it drops below 600 cc. with adequate intake, systemic bacitracin should be stopped. If there are no signs of toxicity in the first week, intramuscular administration may be continued as long as necessary to control the infection. In several instances it has been used continuously for months without evidence of cumulative toxicity, however, it usually can be discontinued safely 3 days after the temperature has returned to normal and all signs of infection have subsided. In the treatment of meningitis, the drug should be continued until the spinal fluid is clear and cultures do not show growth. Intramuscular injection should be used cautiously in patients with known impairment of renal function, even though it has not been observed that toxicity is more likely to develop in such patients than in those with normal kidney function. In some cases in which the infection itself was responsible for a high level of albuminuria and retention of nitrogen, bacitracin has controlled the infection and restored kidney function. The occurrence of mild nephrotoxicity does not necessarily contraindicate continued use of the drug, but it should be discontinued if there is evidence of progressive nitrogen retention or progressive diminution of urinary output. Nephrotoxicity has not been observed following local injection of bacitracin into the central nervous system or into areas of infection or after topical application to the skin, eye or respiratory tract.

Dosage.—In the treatment of systemic infections, bacitracin is administered by intramuscular injection. The total daily dose for adults should not exceed 100,000 units. The usual dose for adults should start with 10,000 to 20,000 units every 8 hours. The initial dose for children is 200 units per kilogram of body weight administered at 8-hour intervals. If there is no response within 48 hours, the dose may be increased to a maximum of 25,000 units for adults or 400 units per kilogram of body weight for children, given every 6 hours. Procaine hydrochloride 2 per cent in isotonic sodium chloride solution may be used as a diluent for solutions injected intramuscularly, using a quantity sufficient to make a concentration of 10,000 units per cubic centimeter. Sites of intramuscular injection should be rotated to avoid painful induration.

In neurosurgical infections, bacitracin is administered by intrathecal, intraventricular, intracisternal or intracerebral injection by dilution with isotonic sodium chloride solution to make a concentration of 1,000 units per cubic centimeter. *Procaine should not be added to solutions for neural injection.* For patients 15 years of age and older, the daily dose by any of the stated intraneural routes is 10,000 units. For infants and young children, the daily dosage varies from 250 to 5,000 units, depending on the particular neural route and the age of the patient.

For infections of the peritoneal cavity, usually due to a mixture of intestinal organisms, 20,000 units of bacitracin in 20 cc. of isotonic sodium chloride solution may be instilled to combat the coccal and clostridial elements of the infection. The same amount may be sprayed over the operative field after resection of the bowel.

... treatment of intestinal amebiasis, 500 to 120,000 units is given in (after meals and at bedtime) for a period of 2 weeks.

For topical application to the skin, instillation in the eye or injection of circumscribed areas of acute infection, the concentration should be 500 to 1,000 units of bacitracin per gram of ointment or per cubic centimeter of solution. Solutions containing 250 or 500 units per cubic centimeter can be employed topically to irrigate wet dressings or the drug may be applied in dry form as a dusting powder. A 1,000-unit per cubic centimeter solution may be diluted with equal parts of 2 per cent procaine hydrochloride for injection into acutely inflamed areas. For intranasal therapy, a solution containing 250 units per cubic centimeter is employed.

ABBOTT LABORATORIES

Ointment Bacitracin: 15, 30 and 113 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

Ophthalmic Ointment Bacitracin: 4 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

COMMERCIAL SOLVENTS CORPORATION

Ointment Bacitracin: 14.2 and 28.4 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

Ophthalmic Ointment Bacitracin: 3.54 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

ELI LILLY & COMPANY

Ointment Bacitracin: 15, 30 and 120 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

Ophthalmic Ointment Bacitracin: 3.75 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

Solvents Bacitracin: 2,500 units.

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

Bacitracin (Sterile): 50,000 unit vials.

Ointment Bacitracin: 14.2 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

Ophthalmic Ointment Bacitracin: 3.5 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

Soluble Tablets Bacitracin: 5,000 units.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Ointment Bacitracin: 14.2 and 28.5 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

Ophthalmic Ointment Bacitracin: 3.54 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

THE UPJOHN COMPANY

Bacitracin (Topical): Vials Powder containing the equivalent of 2,000, 10,000 or 50,000 units of bacitracin

Powder Bacitracin (Topical or Intramuscular): Vials. Each vial contains the equivalent of 2,000, 10,000 or 50,000 units of bacitracin.

BACITRACIN-NEOMYCIN.—See the monograph in the section on antibiotic mixtures.

Carbomycin

CARBOMYCIN.—Magnamycin (PFIZER).—Carbomycin is an antibiotic isolated from the elaboration products of *Streptomyces halstedii*, when grown by deep culture in suitable media. The structural formula of carbomycin has not been established.

Physical Properties.—Carbomycin is a white, odorless, bitter powder, with a melting point between 193 and 220° (with decomposition). It is freely soluble in chloroform and very slightly soluble in water. The approximate amounts that dissolve at 25° in the following solvents to form 100 cc. of solution are: 4 Gm in alcohol and 0.9 Gm in ether. Carbomycin is stable when protected from moisture. The pH of a saturated solution is 5.5 to 8.0.

Actions and Uses.—Carbomycin, a monobasic antibiotic of incompletely defined chemical identity, possesses strong inhibitory activity against certain gram-positive bacteria. Its activity against other types of bacteria and other micro-organisms is under investigation. Until adequate clinical evidence becomes available, carbomycin is indicated only in the treatment of infections caused by staphylococci, pneumococci and hemolytic streptococci. Therefore, it is useful in the treatment of pneumonia, urinary tract infections, soft tissue infections, abscesses and tonsillitis caused by these organisms. Its usefulness in bacteremia and septicemia has not been evaluated completely, but it can be employed in these conditions also when the causative organisms are found to be susceptible on the basis of sensitivity tests.

Carbomycin, as the free base, is only slightly soluble in water but is readily absorbed following oral administration. Blood levels produced following oral administration are not significantly lower than when water-soluble acid salts of the drug are administered by intramuscular injection. An appreciable amount (approximately 10 per cent of the ingested dose) is excreted in the urine in active form, and the drug appears to be distributed in all organs and secretions. The ultimate fate of its soluble salts, the stream. The ultimate portion has not been determined.

Carbomycin exhibits a low degree of toxicity in experimental

animals. Clinically, no harmful side effects have been observed with therapeutically effective doses. Studies of the urine, blood and liver function have revealed no evidence of toxic action. Nausea and vomiting are the principal side effects; diarrhea occurs infrequently. As for all new drugs, close clinical observation for undiscovered toxic effects is desirable, and, for periods of therapy extending beyond 2 weeks, repeated blood counts should be performed. As with other antibiotics, its use may result in overgrowth of *nonsusceptible organisms*, particularly *monilia*. If new infections caused by nonsusceptible bacteria or fungi appear during therapy, the drug should be discontinued and/or appropriate measures instituted.

Dosage.—Carbomycin is administered orally; optimal dosage is still under investigation. For adults, the present total daily dosage is 2 Gm. divided into four equal doses given every 6 hours; in urinary tract infections and in some soft tissue infections, 1 Gm. daily may be adequate. When infections do not respond to 0.5 Gm. every 6 hours, the dosage may be increased to 1 Gm. every 6 hours. Duration of therapy is governed by the clinical response and should be continued until temperature, pulse and respiration have been normal for 48 hours and until other acute manifestations have subsided. Dosage for children is also under study; carbomycin presently is given on the basis of 50 to 100 mg. per kilogram of body weight daily, divided into four equal doses administered at 6-hour intervals.

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

Tablets Magnamycin: 0.1 and 0.25 Gm.

U. S. trademark 568,928.

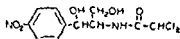
Chloramphenicol

Chloramphenicol is a crystalline nitrobenzene compound now produced synthetically. It is relatively insoluble and, for that reason, usually administered by the oral route. Following a single moderate oral dose of chloramphenicol, maximal blood concentration of the antibiotic is reached within 2 hours, the agent is not detectable in the blood after 8 hours. When multiple doses of chloramphenicol are given, little difficulty is encountered in maintaining high concentrations of the antibiotic in both the blood and the urine. Chloramphenicol appears to be well distributed in the body tissues. It undoubtedly is present in intracellular as well as extracellular body water, since otherwise it would not be so effective in the control of rickettsial infections. It passes over readily into the cerebrospinal and pleural fluids, and appreciable quantities are found in the bile. The placenta offers no barrier to its passage, and the concentration of chloramphenicol in cord blood is approximately 75 per cent of that in the maternal blood within 2 hours after the administration of a single dose. It is as yet unknown whether chloramphenicol passes into the vitreous or aqueous humors. Chloramphenicol is excreted mainly in the urine, in

which appreciable quantities appear within 30 minutes after administration of a single dose.

There are both chemical and biologic tests for the detection of chloramphenicol and its degradation products in body fluids and tissues. Comparison of the two tests on like samples of blood from patients who are receiving chloramphenicol shows that, for the first few hours after the antibiotic has been administered, the tests give comparable results. After this, however, the chemical values rise and the biologic values drop, indicating the conversion of chloramphenicol to an inactive form in the body. In the urine, this difference is always great, the chemical test giving readings about ten times greater than those of the biologic test, another indication that the majority of chloramphenicol that has been excreted is in an inactive form. There is no evidence that renal dysfunction impairs the excretion of chloramphenicol in the urine.

the federal Food and Drug Administration concerning certification of antibiotic drugs" U.S.P. The structural formula of chloramphenicol may be represented as follows:



Physical Properties—Chloramphenicol occurs as fine, white to grayish-white or yellowish-white, needlelike crystals or elongated plates. It is bitter to taste, practically neutral to litmus paper and

Actions and Uses—Chloramphenicol is an antibiotic derived from *Streptomyces venezuelae* or produced synthetically. It is effective against certain gram-negative organisms and against *Rickettsia*.

Because of the occurrence of serious and fatal blood dyscrasias, it is advisable to restrict the use of chloramphenicol to the treatment of typhoid fever and other serious infectious diseases caused by organisms controlled by chloramphenicol but resistant to other antibiotics or other forms of treatment.

The drug is absorbed rapidly from the gastro-intestinal tract and appears promptly in the blood stream after a single oral dose. It is excreted in the urine in high concentration, about 10 per cent being in the active form. The concentration in the spinal fluid is about half of that in the blood.

Chloramphenicol may produce nausea and vomiting. Granulocytopenia and fatal cases of aplastic anemia have been observed

as toxic reactions in the course of therapy with chloramphenicol. Blood studies should be done frequently for all patients receiving this drug.

Dosage.—Initial oral doses of 50 to 75 mg per kilogram of body weight usually are employed. Thereafter, a dose of 0.25 Gm. may be given every 2 to 3 hours. In severe infections, this dose may be increased to 0.5 Gm every 3 hours. The drug should be continued until the temperature is normal and the symptoms have subsided; it then may be given less frequently. In most infections, if the temperature remains normal the drug can be discontinued after 48 hours.

PARKE, DAVIS & COMPANY

Capsules Chloromycetin: 50 and 100 mg.

Kapsoals Chloromycetin: 0.25 Gm.

Ophthalmic Ointment Chloromycetin 1%: 3.54 Gm. tubes. An ointment containing 10 mg. of chloramphenicol in each gram.

Ophthalmic Solution Chloromycetin (*Dried*): 25 mg. vials. A powder containing 25 mg. of chloramphenicol and borate buffer equivalent to 100 mg of boric acid in each vial. To be diluted with distilled water.

U. S. patents 2,483,871, 2,483,884, 2,483,885, 2,483,892.

Chlortetracycline (Aureomycin)

Thus far there are only biologic tests for measuring the absorption, distribution and excretion in body fluids and tissues of chlortetracycline. These give relative values only because chlortetracycline deteriorates in solution, making it difficult to use biologic methods of determination. These tests, as ordinarily performed in clinical laboratories, are so inaccurate that it is not worth while to do them routinely.

Chlortetracycline is administered by its concentration in to 8 hours, and detected in the blood serum for at least 12 hours. When multiple doses are given at 6-hour intervals, concentrations of 2.5 to 20 mcg. are found in the blood serum. Chlortetracycline has been found in emulsions of the liver, kidneys, spleen and lungs of patients who died during chlortetracycline therapy. It is suspected that the antibiotic actually diffuses to explain t assuming not easily

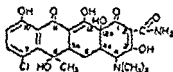
pass the blood brain barrier in human beings, but, when infection of the meninges is present, it is possible to detect it in the cerebrospinal fluid. It passes into the bile in fair concentrations, but as yet it is not known whether it diffuses into the vitreous or aqueous humors. It passes the placental barrier, and appreciable amounts

can be detected in the cord blood of the infant whose mother is receiving chlortetracycline.

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Maximum concentrations of chlortetracycline are obtained within 5 hours after the use of small intramuscular injections. Chlortetracycline produces excellent blood concentrations.

CHLORTETRACYCLINE CALCIUM.—Auroomycin Calcium (LEDERLE).—The calcium salt of 7-chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide. It complies with the requirements of the Federal Food and Drug Administration. The exact chemical formula of chlortetracycline calcium is unknown. It is believed that two of three acid hydrogens of chlortetracycline are replaced by calcium. The structural formula of chlortetracycline may be represented as follows:



Actions and Uses.—Chlortetracycline calcium has the same actions and uses as the hydrochloride salt. See the monograph on chlortetracycline hydrochloride. The calcium salt is given by the oral route.

The calcium salt is given by the oral route to patients in the form of a suspension or syrup. It is not readily absorbed in the form of a dry powder. The dosage for the calcium salt is expressed in terms of the hydrochloride salt.

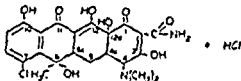
LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

Oral Drops Auroomycin Calcium: 10 and 20 cc. dropper bottles. A suspension containing 100 mg. of chlortetracycline calcium in each cubic centimeter. Preserved with 0.03 per cent methylparaben and 0.02 per cent propylparaben.

Syrup Auroomycin Calcium: 118 and 473 cc. bottles. A syrup containing 51 mg. of chlortetracycline calcium in each cubic centimeter. Preserved with 0.03 per cent methylparaben and 0.02 per cent propylparaben.

CHLORTETRACYCLINE HYDROCHLORIDE-U.S.P.—Aureomycin Hydrochloride (**LENEXE**).—Aureomycin Hydrochloride—The hydrochloride of 7-chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,8,11-tetrahydro-2H-pyrido[2,1-b][1,4]diazepine-2-carboxylic acid.

U.S.P. The structural formula of chlortetracycline hydrochloride may be represented as follows:



Physical Properties—Chlortetracycline hydrochloride is an odorless, yellow, crystalline powder with a bitter taste. It is stable in air but may be affected by light. It is soluble in solutions of the alkali hydroxides and their carbonates but practically insoluble in acetone, chloroform, dioxan and ether.

Actions and Uses.—In vitro, chlortetracycline hydrochloride is effective against certain strains of beta hemolytic streptococci, non-hemolytic and hemolytic streptococci of group D, alpha hemolytic streptococci, pneumococci, staphylococci, *Escherichia coli*, *Aerobacter aerogenes*, *Klebsiella pneumoniae*, *Bacillus subtilis* and *Corynebacterium hoffmanni*. In embryonated eggs it kills rickettsiae and certain large viruses.

[illegible]

obtained with penicillin). In infections produced by meningococci, spirochetes and *Cl welchii* chlortetracycline is effective but penicillin is still the antibiotic of choice. In infections produced by *Staph aureus*, *Str. fecalis*, *L. monocytogenes*, the *Bacteroides* and *Lept. icterohemorrhagica* chlortetracycline has proved effective. Chlortetracycline with a pyrimidine derivative of sulfanilamide is of value in meningitis caused by *Hemophilus influenzae*. Chlortetracycline hydrochloride is highly effective in the local treatment of vaginitis produced by *Trichomonas vaginalis*. It may also be used in staphylococcic and pneumococcic infections, in acute brucellosis, the *Shigella* group of infections and in subacute bacterial endocarditis produced by certain gram-positive or gram-negative bacteria.

Chlortetracycline hydrochloride may be used for the suppression of bacterial growth in the stool as a preoperative and postoperative prophylactic measure in surgery of the large bowel. Chlortetracycline has proved effective as a prophylactic in puerperal sepsis.

Chlortetracycline hydrochloride should not be used in the treatment of infections produced by *Proteus vulgaris* or *Pseudomonas aeruginosa* except in the occasional strains of these organisms that are sensitive to its antibiotic effects. Clinical reports indicate that chlortetracycline hydrochloride is a beneficial therapeutic agent in the treatment of certain patients ill with whooping cough. It is of limited value in typhoid fever and its usefulness in other infections caused by species of *Salmonella* remains to be determined by further study.

The drug, suitably buffered, may be used locally in the eye against a variety of ocular viral infections, such as inclusion conjunctivitis, follicular conjunctivitis and ocular bacterial infections caused by susceptible organisms.

Chlortetracycline hydrochloride, in a suitably buffered solution, may be administered intravenously to hospitalized patients unable to take the drug by mouth. Because of the danger of thrombophlebitis at the site of injection, intravenous therapy should be discontinued as soon as oral administration can be resumed.

The drug produces nausea, vomiting and diarrhea in some patients.

Dosage.—The minimum daily oral dose for the average adult is 1 Gm divided into four 0.25 Gm doses. Children should receive proportionately less, for example, a child weighing 20 Kg (about 44 lb.) may be given 50 mg. four or five times daily. In the absence of a clinical response within 24 hours or for acutely ill patients, the total number of daily doses (0.25 Gm), rather than the size, should be increased on the second or third day, as individual doses exceeding 0.25 Gm are not absorbed efficiently.

Solutions for ophthalmic use may be prepared by adding 5 cc. of sterile distilled water to 25 mg. of the hydrochloride. One or two drops in the affected eye every 2 hours usually suffices to control the condition.

A solution buffered with sodium glycinate, and containing not more than 100 mg. of chlortetracycline hydrochloride per 10 cc. of sterile diluent, is administered intravenously on the basis of 20 to 25 mg. per Kg. of body weight every 24 hours. This daily dosage

should be divided into two, three or four injections given at 4, 6, 8 or 12 hr. intervals. The solution should be prepared by adding 10 cc. of the drug to 10 cc. of the buffer, and the contents shaken vigorously for at least 1 minute to ensure solution prior to administration. To avoid reactions, approximately 5 minutes should elapse for the injection of each 10 cc. of solution.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

Aureomycin Hydrochloride: Vials with dropper containing 25 mg. of chlortetracycline hydrochloride, 62.5 mg. of sodium chloride and 25 mg. of sodium borate, to be diluted with distilled water for ophthalmic use.

Capsules Aureomycin Hydrochloride: 50, 100 and 250 mg.

Ointment Aureomycin Hydrochloride (Ophthalmic) 1%: 3.5 Gm. tubes. An ointment containing 10 mg. of chlortetracycline hydrochloride in each gram.

Powder Aureomycin Hydrochloride (Intravenous): 10 and 50 cc. vials. A powder containing 0.1 and 0.5 Gm., respectively, of chlortetracycline hydrochloride. Buffered with sodium glycinate.

Spersoids Aureomycin Hydrochloride: 36 and 75 Gm. bottles. A flavored powder containing 16.7 mg. of chlortetracycline hydrochloride in each gram.

Soluble Tablets Aureomycin Hydrochloride: 50 mg.

Erythromycin

ERYTHROMYCIN-U.S.P.—Ilotycin (Lilly).—"Erythromycin is an antibacterial substance produced by the growth of *Streptomyces erythreus* Waksman. It contains not less than 85 per cent of erythromycin calculated on the anhydrous basis." *U.S.P.* The structural formula of erythromycin has not been established.

Physical Properties.—Erythromycin is a white or slightly yellow, odorless, bitter, crystalline powder, with a melting point between 133 and 138°. It is freely soluble in alcohol and ether and very slightly soluble in water. Erythromycin is slightly hygroscopic. The pH of a saturated solution is 8.0 to 10.5. A pH of less than 4 is highly destructive to the antibiotic.

Actions and Uses.—Erythromycin is clinically effective against certain infections caused by gram-positive bacteria. These include

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against other gram-positive micro-organisms such as alpha-hemo-

lytic and nonhemolytic streptococci or against gram-negative bacteria such as meningococci and gonococci. In vitro evidence indicates that staphylococcal resistance to erythromycin may develop in a manner similar to that of the other antibiotics. The drug is as active against susceptible penicillin-resistant strains as it is against penicillin-sensitive strains. Erythromycin also is useful for the treatment of acute and chronic intestinal amebiasis.

Erythromycin may produce mild gastro-intestinal disturbances. Thus far, such side effects are infrequent and seem to be related to dosage; large doses occasionally cause nausea, vomiting, diarrhea and prostration. Erythromycin rarely induces the profound change in intestinal flora encountered with prolonged use of broad-spectrum antibiotics. Contraindications thus far have not developed, but until there has been longer experience in its use, physicians should be alert to the appearance of untoward reactions. When therapy is prolonged more than 2 weeks, repeated blood counts are advisable.

Dosage.—Currently, erythromycin is administered only by the oral route. With specially coated tablets, the drug may be taken with or without meals. In this form, a single dose of 0.2 Gm produces an average blood concentration of 0.04 to 0.16 mcg per cubic centimeter for 6 to 8 hours.

Optimal dosage has not been finally established for susceptible bacterial infections. The average effective dosage for adults ranges from 0.2 to 0.5 Gm every 6 hours; for children, doses of 6 to 8 mg. per kilogram of body weight every 6 hours are suggested. Pneumococcus pneumoniae has responded to doses of 0.2 Gm initially and 0.1 Gm every 3 hours. In severe infections, doses up to 0.5 Gm may be repeated every 6 hours if necessary. Doses in excess of 0.5 Gm, administered every 6 hours, occasionally have produced nausea, vomiting and diarrhea. For intestinal amebiasis, the suggested dosage is 15 mg per kilogram of body weight daily, administered in divided doses for a period of 14 days.

ELI LILLY & COMPANY

Tablets Ilotycin (*Specially Coated*): 0.1 Gm.

THE UPJOHN COMPANY

Tablets Erythromycin (*Specially Coated*): 0.1 Gm.

ERYTHROMYCIN ETHYL CARBONATE—Ilotycin Ethyl Carbonate (Lilly)—Erythromycin ethyl carbonate is the ethyl carbonate ester of erythromycin, an antibacterial substance produced by the growth of *Streptomyces erythreus* Waksman. The structural formula of erythromycin ethyl carbonate has not been established.

Physical Properties.—Erythromycin ethyl carbonate is a white, odorless powder having a slightly bitter taste. It is freely soluble in alcohol and practically insoluble in water. The amount that dissolves in ether to form 100 cc of solution is about 4.7 Gm.

Actions and Uses.—Erythromycin ethyl carbonate, a salt of erythromycin, shares the actions and uses of the parent antibiotic. (See the monograph on erythromycin.) The ethyl carbonate salt

is suitable for the extemporaneous preparation of flavored suspensions of the drug for oral administration.

Dosage.—Erythromycin ethyl carbonate is administered orally in doses expressed in terms of erythromycin base. For adults, a dose of 200 mg. of erythromycin every 4 to 6 hours is considered adequate. The optimal dosage for children has not been finally determined, but a dose of 11 mg. of erythromycin equivalent per kilogram (about 5 mg. per pound) of body weight administered every 6 hours is considered reasonable.

ELI LILLY & COMPANY

Oral Suspension Ilotycin Ethyl Carbonate: 75 cc. bottles. A powder with added flavoring for suspension in distilled water to give a mixture containing 20 mg. of erythromycin as the ethyl carbonate in each cubic centimeter.

ERYTHROMYCIN GLUCOHEPTONATE.—Ilotycin Glucoheptonate (LILLY).—Erythromycin glucoheptonate is the glucoheptonate salt of erythromycin, an antibacterial substance produced by the growth of *Streptomyces erythreus* Waksman. The structural formula of erythromycin glucoheptonate has not been established.

Physical Properties.—Erythromycin glucoheptonate is a white, crystalline, odorless powder. It is freely soluble in water and alcohol and practically insoluble in ether. The pH of a 2 per cent solution is between 6.0 and 7.5.

Actions and Uses.—Erythromycin glucoheptonate has the same actions and uses as the base except that it is primarily suited for intravenous injection. (See Parenteral administration in infections in patients who are unable for any other such cases oral medication was resumed as soon as the patient can ingest and retain it.)

Dosage.—For intravenous injection, an initial solution should be prepared by completely dissolving the equivalent of 0.25 Gm. of erythromycin base in not less than 10 cc. of water for injection—U.S.P. This solution retains its potency for 7 days if kept in a refrigerator. *Saline or other diluent should not be employed for making the initial solution in order to avoid gel formation or slow and incomplete solution of the drug.* For adults, the initial solution should be added to 250 to 500 cc. of isotonic sodium chloride solution or 5 per cent dextrose solution and administered by slow intravenous infusion for 20 to 60 minutes. This dose (0.25 Gm. equivalent to the base) may be repeated every 6 hours. A continuous slow infusion, administering the equivalent of 1 to 2 Gm. of the base over a 24-hour period, may be employed as an alternate method. For children, the initial solution is diluted as for adults, but is administered in doses calculated on the basis of the equivalent of 11 mg. of the base per kilogram (about 5 mg. per pound) of body weight, every 6 hours. Although the initial solution may be used for intravenous injection over a 5-minute period without severe reactions, this is not recommended because of nausea, vomit-

ing or pain along the vein; thrombosis has occurred in some instances

ELI LILLY & COMPANY

Powder Erythycin Glucoheptonate: 20 cc. vials. Each vial contains the equivalent of 0.25 Gm. of erythromycin as the glucoheptonate salt

ERYTHROMYCIN LACTOBIONATE.—Erythrocin Lactobionate (Abbott).—Erythromycin lactobionate is the lactobionate salt of erythromycin, an antibacterial substance produced by the growth of *Streptomyces erythreus* Waksman. The structural formula of

white, prac-
and alcohol
it solution is

Actions and Uses.—Erythromycin lactobionate, a water-soluble salt of erythromycin suitable for intravenous or intramuscular injection, has the same actions and uses as the base. (See the monograph on erythromycin.) Injection of the drug is indicated in patients unable to tolerate oral medication or in whom high

Dosage.—Erythromycin lactobionate is administered either intravenously or intramuscularly, preferably by the former route to avoid pain produced by the latter route. Dosage is expressed in terms of erythromycin base. The usual dosage for children and adults is 2.2 to 4.4 mg. per kilogram (1 to 2 mg. per pound) of body weight either intravenously or intramuscularly, injected at intervals of 8 to 12 hours.

A 5 per cent "stock" solution (equivalent to 50 mg. of erythromycin base per cubic centimeter) first should be prepared by completely dissolving the equivalent of 0.3 Gm. of erythromycin base in 6 cc. (or the equivalent of 1 Gm. of base in 20 cc.) of either water for injection or 5 per cent dextrose solution. *Isotonic sodium chloride solution (normal saline) or other inorganic salt solutions should never be used as a solvent for preparing the 5 per cent "stock" solution of erythromycin lactobionate because they cause precipitation of the active ingredient at that concentration.* In the dry form the salt is stable at ordinary temperatures for prolonged periods, the 5 per cent solution is stable for 2 weeks when stored in a refrigerator.

For intravenous injection, the 5 per cent solution should be diluted with not less than four volumes of either 5 per cent dextrose or isotonic sodium chloride solution to make a final concentration of not more than 1 per cent (equivalent to 10 mg. of erythromycin

base per cubic centimeter). Intravenous injection of the calculated dose should be given slowly over a period of not less than 5 minutes to avoid pain along the course of the vein; alternatively, the calculated intravenous dose may be administered by infusion by diluting this in 200 to 500 cc. of 5 per cent dextrose or isotonic sodium chloride solution.

For intramuscular injection, the 5 per cent "stock" solution is employed without further dilution. The calculated dose should be injected deeply into a large muscle with extreme care to avoid subcutaneous deposition. Pain follows intramuscular injection, but this has been associated only with transitory local irritation. A single intramuscular dose should not exceed 0.5 Gm., as a precaution against the production of tissue damage.

ABBOTT LABORATORIES

Powder Erythrocin Lactobionate: 10 and 30 cc. vials. Each vial contains the equivalent of 0.3 and 1 Gm., respectively, of erythromycin as the lactobionate salt. Preserved with 0.9 per cent benzyl alcohol.

ERYTHROMYCIN STEARATE.—Erythrocin Stearate (ABBOTT).—Erythromycin stearate is the stearic acid salt of erythromycin. It usually contains some uncombined stearic acid. The structural formula of

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stearate dissolves in 100 cc. of ether.

Actions and Uses.—Erythromycin stearate has the same actions and uses as erythromycin base. (See the monograph on erythromycin.) The stearate salt, when properly buffered, gives blood levels comparable to those obtained with the base.

Dosage.—Erythromycin stearate is administered orally. The dosage is expressed in terms of, and is identical with, the base. (See the monograph on erythromycin.) For children, the recommended dose is 4.5 to 6.5 mg. of erythromycin base per kilogram (2 to 3 mg. per pound) of body weight, administered at 4-hour to 6-hour intervals.

ABBOTT LABORATORIES

Oral Suspension Erythrocin Stearate (Pediatric): 60 cc. bottles. A flavored suspension containing 20 mg. of erythromycin as the stearate in each cubic centimeter. Preserved with 0.1 per cent methylparaben and 0.02 per cent propylparaben.

Filmtabs Erythrocin Stearate: 0.1 and 0.2 Gm. Each tablet contains the equivalent of 0.1 or 0.2 Gm. of erythromycin base.

U. S. trademark 590,748.

Neomycin

BACITRACIN-NEOMYCIN.—See the monograph in the section on antibiotic mixtures.

NEOMYCIN SULFATE-U.S.P.—Mycilradin Sulfate (UPJOHN)—"Neomycin Sulfate is the sulfate of an antibacterial substance produced by the growth of *Streptomyces fradiae* Waksman. It contains an amount of neomycin sulfate equivalent to not less than 60 per cent of neomycin base, calculated on the dried basis" U.S.P.

Physical Properties.—Neomycin sulfate occurs as white to slightly yellow crystals or powder. It is odorless or practically odorless and is hygroscopic. Its solutions are dextrorotatory. One gram dissolves in about 1 cc. of water. It is very slightly soluble in alcohol, and is insoluble in acetone, chloroform and ether.

Actions and Uses.—Neomycin sulfate is a polybasic compound, thermostable and soluble in water but insoluble in organic solvents. It differs from other antibacterial agents in that it is extremely stable and very active in alkaline solution. Neomycin is not inactivated by exudates, enzymes, gastro-intestinal secretions and by-products of digestion or bacterial growth. The sulfate salt is stable in the dry state for at least 2 years when stored at room temperature. Prepared solutions retain their potency for at least 1 year at room temperature, although there may be a progressive deepening of color of solutions stored at room temperature or 37°. Refrigeration of neomycin solutions, therefore, is recommended.

Neomycin sulfate exhibits activity against a variety of gram-positive and gram-negative bacteria. In the former group, it appears to be more effective against staphylococci than streptococci. It has a wider antibacterial spectrum than bacitracin, penicillin or streptomycin, and it is sometimes effective against *Pseudomonas* and *Proteus* infections. Micro-organisms resistant to neomycin have been demonstrated *in vitro*, but emergence of resistant strains has not yet been observed clinically. It may be effective against micro-organisms that have developed resistance to streptomycin; however, the evidence thus far available does not justify the conclusion that neomycin suppresses the overgrowth of resistant bacterial variants. It is not active against fungi.

Neomycin sulfate is useful for topical application as a solution or ointment in the local treatment or prevention of susceptible infections of the skin and the eye, including pyogenic or secondarily infected stasis dermatoses, impetigo, wounds, burns, ulcers (varicose or trophic), conjunctivitis, blepharitis and sty (hordeolum). A solution is considered superior to an ointment in treating trophic ulcers and secondarily infected burns. In severe or extensive infections, local therapy should be supplemented with sulfonamides by mouth or penicillin by injection.

Neomycin sulfate also is useful as an intestinal antiseptic by oral administration for suppression of the usual bacterial inhabitants of the colon in surgery of the large bowel and anus. Because of its poor absorption from the gastro-intestinal tract, it rarely produces systemic action or toxic effects when administered orally. The small fraction absorbed (about 3 per cent of the amount ingested) is rapidly excreted in the urine, the remainder is excreted unchanged in the feces. Divided total daily oral dosage not exceeding 6 to 10 Gm. for 1 to 3 days produces blood levels lower than the toxic serum concentration of 0.2 mg. per cubic centimeter. Outgrowth

of nonpathogenic yeasts usually follows reduction of the bacteria flora of the colon; *Aerobacter aerogenes* may grow out about 12 hours following the outgrowth of yeasts. The effectiveness of neomycin is variable in suppressing organisms of the Clostridia group.

Neomycin sulfate is further useful parenterally in solution for intramuscular injection of hospitalized patients for the treatment of serious systemic infections caused by gram-negative microorganisms, particularly *K. pneumoniae*, *H. influenzae*, *P. vulgaris* or *Ps. aeruginosa*, and of urinary tract infections caused by *Ps. aeruginosa*, *E. coli*, *P. vulgaris* or *A. aerogenes*, when such infections are resistant to other antibiotic and chemotherapeutic agents that are less toxic parenterally. Its effectiveness against systemic staphylococci, or streptococci or other gram-positive infections has not been established.

Neomycin sulfate usually is well tolerated and is relatively non-irritating for topical use. It is reported to have a low index of sensitization. A mild laxative effect occurs with oral administration. Prolonged oral therapy may result in overgrowth of non-susceptible organisms—particularly *Candida*. If new infections caused by bacteria or fungi appear during therapy, it may be advisable to discontinue the drug and/or institute appropriate measures to combat them. Oral use as an intestinal disinfectant is contraindicated in the presence of obstruction.

Parenteral use should be restricted to intramuscular injection within specific dosage limits because of the danger of nephrotoxic and ototoxic effects that may be produced by dosages above 0.2 mg. per kg. body weight. It is also reported that high dosages may be associated with mild albuminuria, decreased urinary output, and that discontinuance of the drug may be necessary to restore auditory function of the ear. Therefore, the dosage that produced by streptomycin, therefore, is necessary.

development of these toxic effects. The urine and blood should be examined for evidence of renal impairment, and audiometric tests should be made for evidence of hearing impairment, prior to and during the course of parenteral therapy with neomycin. Audiometric tests are particularly important in patients with a history of previous streptomycin or dihydrostreptomycin therapy. When administered in accordance with the dosage limits indicated, intramuscular injections do not produce clinical signs of toxicity.

Neomycin sulfate may be administered topically, orally for intramuscularly for systemic

For external use, it is applied as a solution containing 5 mg. per cubic centimeter or as an ointment containing 5 mg. per gram.

The solution is used for wet dressings, packs, irrigations or instillation. Topical applications of the solution or ointment are made once or twice daily, using an amount sufficient to cover the affected region.

For preoperative disinfection of the colon, the patient is placed on a low residue diet and, immediately following the administration of a cathartic (unless otherwise contraindicated), is given an oral dose of 1 Gm every hour for four doses followed thereafter by 1 Gm. every 4 hours for 24 to 72 hours prior to surgery. Administration of the antibiotic should not extend beyond 72 hours. This amount usually produces four to eight bowel movements.

For intramuscular injection, a solution containing 200 or 250 mg. per cubic centimeter is employed. The dosage is calculated on the basis of 10 to 15 mg per kilogram of body weight per day, and should not exceed 15 mg per kilogram or a total of more than 1 Gm daily. The total daily amount should be divided into four equal doses injected every 6 hours. Intramuscular injection should not be continued for longer than 10 days and otherwise should be discontinued as soon as susceptible infections resistant to other less toxic forms of therapy are brought under control or are found to be resistant to neomycin therapy.

ELI LILLY & COMPANY

Ointment Neomycin Sulfate: 14.2, 28.35 and 113.4 Gm. tubes. An ointment containing 5 mg of neomycin sulfate in each gram.

Ophthalmic Ointment Neomycin Sulfate: 3.54 Gm. tubes. An ointment containing 5 mg of neomycin sulfate in each gram.

THE UPJOHN COMPANY

Powder Mycifradin Sulfate: Vials containing 0.5 Gm. of neomycin sulfate.

Tablets Mycifradin Sulfate: 0.5 Gm.

U. S. trademark 592,157.

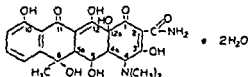
Oxytetracycline (Terramycin)

At present there is no chemical test for measuring oxytetracycline in the body fluids or tissues. Hence, studies of its absorption, distribution and excretion in the man being treated are being conducted.

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..... doses is satisfactory for the maintenance of adequate concentrations in the blood. The antibiotic appears in emulsions of most of the organs of animals which have been given standard therapeutic doses, and it is believed that it diffuses into cells. Oxytetracycline sometimes is detected in the spinal fluid following administration to normal individuals, particularly if the meninges are inflamed. It diffuses into pleural and abdominal fluids and passes the pla-

central barrier easily. High concentrations of a biologically active form are excreted in the bile, stool and urine. There is no evidence that renal dysfunction interferes with the excretion of oxytetracycline. Metabolic studies of the degradation of oxytetracycline in the body have not yet been reported.



Physical Properties.—Oxytetracycline is a dull yellow, odorless, slightly bitter crystalline powder. It melts between 179 and 182° (with decomposition). It is soluble in acids and alkalis, very slightly soluble in acetone, alcohol, chloroform and water and practically insoluble in ether.

Actions and Uses.—Oxytetracycline is isolated from the elaboration products of the actinomycete, *Streptomyces rimosus*, when the micro-organism is grown on suitable culture media. As the base, it is suitable for oral administration for the same purposes as the more soluble oxytetracycline hydrochloride. (See the general statement on oxytetracycline and the monograph on oxytetracycline hydrochloride.) Clinical studies of serum levels indicate that absorption of the base is approximately comparable to that of the hydrochloride after oral administration of equal doses of either form. Significant differences in side reactions have not been observed.

Dosage.—Oxytetracycline, as the base, is administered in the same doses as specified for oxytetracycline hydrochloride, since the latter also is expressed in terms of the base. See the monograph on oxytetracycline hydrochloride.

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

Pediatric Drops Terramycin: 1 Gm. vials. A powder with added flavoring for suspension in water to give a solution containing 100 mg. of oxytetracycline in each cubic centimeter.

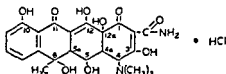
Oral Suspension Terramycin: 1.5 Gm. vials. A powder with added flavoring for suspension in distilled water to give a solution containing 50 mg. of oxytetracycline in each cubic centimeter.

Tablets Terramycin. 50 mg., 0.1 and 0.25 Gm.

U. S. trademark 577,504.

OXYTETRACYCLINE HYDROCHLORIDE—U.S.P.—Terramycin Hydrochloride (Pfizer).—Hydrochloride of 4-dimethylamino-1,4,4a,5,

5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide. The structural formula of oxytetracycline hydrochloride may be represented as follows.



Physical Properties.—Oxytetracycline hydrochloride is a yellow, crystalline, odorless powder with a bitter taste. It melts with decomposition between 190 and 194°. It is very soluble in water, soluble in alcohol, sparingly soluble in acetone, slightly soluble in chloroform and very slightly soluble in benzene and ether. The pH of a 1 per cent solution of oxytetracycline hydrochloride is about 2.5.

Actions and Uses.—Oxytetracycline hydrochloride is bacteriostatic or bactericidal, depending on its concentration. In vitro, it is effective against most strains of such common pathogens as beta-hemolytic streptococci, nonhemolytic streptococci, alpha-hemolytic streptococci, pneumococci, staphylococci, *Bacterium (Escherichia) coli*, *Aerobacter aerogenes*, *Klebsiella pneumoniae*, *Bacillus subtilis* and *Hemophilus influenzae*. In embryonated eggs it kills rickettsiae and certain large viruses.

monia, psittacosis, acute trachoma, lymphogranuloma venereum; nonspecific urethritis, beta-hemolytic streptococcal infections; bacillary infections caused by *A. aerogenes*, *B. coli* and *K. pneumoniae*, bacillary dysentery, and urinary tract infections produced by *B. coli*, *A. aerogenes*, staphylococci and streptococci. It is also effective in acute laryngotracheobronchitis, acute infectious croup (nondiphtheritic), acute bronchitis and bronchiolitis, otitis media and mastoiditis (with or without surgical therapy, in accordance

rheal ophthalmia (penicillin is ordinarily the antibiotic of choice, but oxytetracycline is useful in patients who are allergic to penicillin). Oxytetracycline is effective in certain stages of syphilis (a use of particular import in patients allergic to penicillin, but its value relative to that of penicillin is a question requiring further study) and also in chancroid, granuloma inguinale and yaws (results in yaws appear to be equal to those obtained with penicillin). In infections caused by meningococci, spirochetes (including Vincent's infection in addition to the spirochetal diseases already men-

tioned) and *Clostridium welchii*, oxytetracycline is effective but penicillin is still the antibiotic of choice (except in patients allergic to penicillin). In infections produced by *Micrococcus pyogenes* (*Staphylococcus aureus*), *Streptococcus fecalis* and other species

of streptococci, in meningitis caused by *Haemophilus influenzae*. Oxytetracycline hydrochloride is highly effective in the local treatment of vaginitis produced by *Trichomonas vaginalis*. It is useful also in staphylococcic and pneumococcic infections, in brucellosis, in infections caused by species of *Shigella* and in bacterial endocarditis produced by susceptible strains of gram-positive or gram-negative bacteria.

Oxytetracycline may be used for the suppression of the colonic bacterial flora as a preoperative and postoperative prophylactic measure in surgery of the large bowel. It also has proved effective in the prophylaxis and treatment of puerperal sepsis.

Oxytetracycline is effective against only some strains of *Proteus vulgaris* and *Pseudomonas aeruginosa* and should not be used in systemic infections produced by these organisms unless sensitivity tests have demonstrated probable effectiveness. Clinical reports indicate that oxytetracycline is a beneficial therapeutic agent in the treatment of whooping cough, particularly when given in the preparoxysmal stage of the disease. It is of limited value in typhoid fever, and its usefulness in other infections caused by species of *Salmonella* remains to be determined by further study.

Oxytetracycline is useful in conjunction with streptomycin in the chemotherapy of tuberculosis, to delay the emergence of microbial resistance to streptomycin in patients unable to tolerate, or infected with organisms resistant to, aminosalicylic acid or isoniazid.

For systemic distribution, this antibiotic usually is administered orally but may be administered intravenously or intramuscularly to patients unable to take it by mouth. In such cases, the intravenous route, particularly, is indicated in the treatment of infections so fulminating as to call for immediate high antibiotic levels in the blood and tissues (notably in peritonitis), and the intramuscular route is appropriate in the treatment of infections not of such urgency. Parenteral therapy should be supplanted by oral

(particularly lesions not penetrated by the blood) are useful for instillation of the urethra in the local treatment of chronic nonspecific urethritis. Also in suitably buffered solution, the antibiotic may be used locally in the eye against a variety of ocular viral infections, such as inclusion conjunctivitis, for administration.

Dosage.—The dosage of oxytetracycline hydrochloride required for an optimal effect varies in accordance with the severity, response and susceptibility of the particular infection. In the average adult, the suggested minimum daily dose for oral administration is 1 Gm. Higher daily doses (2 Gm or more) may be required in severe infections or in patients who do not respond rapidly to lower dosages. As much as 4 Gm daily is absorbed and tolerated well in the treatment of patients with very severe infections. The total daily dose should be administered in four equal portions given at 6-hour intervals. Administration with cold milk or a light meal helps to increase upper gastro-intestinal tract tolerance. The total daily dose for children is proportionately less than for adults. In severe infections in children, 25 to 40 mg per kilogram (11.5 to 18 mg per pound) of body weight daily should be adequate.

To delay the emergence of microbial resistance to streptomycin in the therapy of tuberculosis, oxytetracycline is administered orally in a dosage of 1 Gm daily to replace aminosalicylic acid, isoniazid or other antituberculosis agents in patients unable to tolerate these drugs or infected with organisms resistant to them.

As a guide to therapy, the high urinary and intestinal concentrations of the antibiotic following oral administration and its stability in the body fluids should be taken into consideration. Duration of therapy should be for at least 24 to 48 hours after symptoms and fever have subsided.

Certain diseases are treated in courses, such as 10 days for intestinal amebiasis and 7 days for pinworm infestation; bacterial endocarditis requires therapy for 6 to 8 weeks or longer, the duration of treatment being guided by bacteriologic and clinical response with appropriate follow-up observations. A dose of 1 Gm, administered in two 0.5 Gm portions at 6-hour intervals, is sufficient to cure 98 per cent of acute gonococcal infections. In primary and secondary syphilis, 1 to 2 Gm daily by mouth in divided doses for 8 to 15 days has given good results.

The specially constituted preparation for intravenous administration is dissolved in sterile distilled water, isotonic saline solution or 5 per cent dextrose solution and further diluted with the solvent so that the final volume (containing 0.25 or 0.5 Gm of oxytetracycline) is at least 100 cc. The solution should be administered at a rate not exceeding 100 cc per 5 minutes. In adults, 0.5 to 1 Gm daily, administered intravenously in divided doses at 12-hour intervals, should be adequate for the treatment of most acute infections, and a dose of 2 Gm daily should not be exceeded in severe infections. For children, 10 to 20 mg per kilogram (4.5 to 9 mg per pound) of body weight daily by this route is generally adequate.

The specially constituted preparation for intramuscular administration is dissolved in sterile distilled water or isotonic saline to yield a solution that contains 40 mg each of oxytetracycline and magnesium chloride together with 2 per cent procaine hydrochloride. Not more than 2 cc of this solution should be injected into a given site at one time. For the treatment of most acute infections of mild or moderate severity, the intramuscular dosage is 0.2 to 0.3 Gm daily, injected in divided doses of 0.1 Gm at 8-hour to

12-hour intervals. This intramuscular dosage provides about the same blood and tissue levels as 1 to 2 Gm. per day given orally.

Parenteral administration, whether intravenous or intramuscular, should be employed only when the oral route is not feasible and should be supplanted by oral administration as soon as practicable.

For local therapy of susceptible ocular infections, the specially constituted preparation for ophthalmic use is dissolved in sterile distilled water to yield a 0.5 per cent solution (5 mg. per cubic centimeter). One or two drops of this solution is instilled into the conjunctival sac four to six times daily. A 2.5 per cent solution (25 mg. per cubic centimeter in normal saline) of the preparation specially constituted for intravenous administration may be used by direct injection.

For local infection;

of this solution is

minutes, either daily or every other day, for a total of not more than seven instillations.

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

Capsules Terramycin Hydrochloride: 50, 100 and 250 mg. Each capsule contains the equivalent of 50, 100 or 250 mg., respectively, of oxytetracycline as the hydrochloride.

Terramycin Hydrochloride (Intravenous): Vials containing the equivalent of 0.25 and 0.5 Gm. of oxytetracycline as the hydrochloride. Buffered with 1 and 2 Gm. of ascorbic acid, respectively.

Terramycin Hydrochloride with Magnesium Chloride 5% and Procaine Hydrochloride 2% (Intramuscular): 3 cc. vials. When diluted with 21 cc. of sterile aqueous diluent each cubic centimeter contains 50 mg. of oxytetracycline as the hydrochloride with 50 mg. of magnesium chloride hexahydrate and 20 mg. of procaine hydrochloride.

Ophthalmic Solution Terramycin Hydrochloride: Bottles containing the equivalent of 25 mg. of oxytetracycline as the hydrochloride with 62.5 mg. of sodium chloride. Buffered with 25 mg. of sodium borate. To be diluted with 5 cc. of distilled water.

Oral Drops Terramycin Hydrochloride: 10 cc. dropper bottles. A flavored alcohol solution containing the equivalent of 0.2 Gm. of oxytetracycline as the hydrochloride in each cubic centimeter (approximately 50 mg. in each nine drops). The oxytetracycline hydrochloride and diluent are packaged together in separate containers to be mixed before using.

U. S. patent 2,516,080 U. S. trademark 577,504

OXYTETRACYCLINE-POLYMYXIN B.—See the monograph in the section on antibiotic mixtures.

Penicillin

Penicillin is an antibiotic substance, existing in several forms, that is derived from certain species of molds belonging to the genus

Penicillium by extraction of cultures grown on special media. The various forms of penicillin, so far isolated, have been designated as F, G, K, O and X.

Amorphous mixtures formerly were employed widely in the form of their sodium or calcium salts. Crystalline preparations of greater purity and stability, containing more than one kind of penicillin or containing chiefly penicillin G as either the sodium or potassium salt, are now used in the majority of instances. Penicillin O is allylmercaptomethyl penicillin produced by growing the mold in a medium containing allylmercaptoacetic acid.

Penicillin mixtures for parenteral or oral use are limited by the Food and Drug Administration to a content of not more than 30 per cent of penicillin K. Topical forms are not restricted as to content. Crystalline penicillin is defined by the Food and Drug Administration as the heat-stable crystalline (sodium or potassium) salt of one or more kinds of penicillin, it must be capable of withstanding exposure to 100° for 4 days. Amorphous and crystalline mixtures are required to have a potency of not less than 500 units per milligram. Crystalline preparations designated as Crystalline Penicillin G are required to contain 90 per cent of G, determined by the N-ethylpiperidine method, the sodium salt to have a potency of not less than 1,500 units per milligram, the potassium salt a potency of not less than 1,435 units per milligram. One unit is defined as the penicillin activity contained in 0.6 mcg. of the Food and Drug Administration master standard and is approximately equivalent to the original Oxford unit. Potency is assayed by bacteriologic testing against a strain of *Staphylococcus aureus* or other suitable organism.

plete absorption from the gastro-intestinal tract. This means that a considerable amount of penicillin may be excreted in the stool. This observation coupled with those that show that penicillin, except in the form of the complex salt benzathine penicillin G, is destroyed by gastric juice in the stomach and by penicillinase produced by many strains of *E. coli* in the large bowel, make it clear that the administration of penicillin by the oral route is an uncertain therapeutic procedure.

When aqueous solutions of crystalline penicillin G are administered by the intravenous route, peak concentrations are reached in the blood in a few minutes, and then the blood levels begin to fall. Following intramuscular injection, maximal concentrations are reached in 30 to 60 minutes. Subcutaneous injections are absorbed at a more variable rate, but peak concentrations generally are reached in about 60 minutes. Following the injection of penicillin by any of these routes, maximal concentrations are reached quickly, and the blood level of the antibiotic falls rapidly if renal function is normal. Only traces may be found within 3 or 4 hours after injection. For this reason, a 3-hour schedule ordinarily has been advised for intramuscular administration of crystalline penicillin G,

and 2-hour schedules seem advisable in the treatment of certain patients.

Penicillin given by inhalation is absorbed rapidly and curves of its concentration in the blood resemble those observed following intramuscular injection. Systemic diffusion of crystalline penicillin administered by the intrathecal, intrapleural or intrapericardial routes is much slower, and easily detectable quantities of the antibiotic may be found in the spinal, pleural or pericardial fluid for 12 to 24 hours after single doses. This is also true when penicillin is injected into synovial cavities, but apparently is not the case when it is injected into the peritoneal cavity, from which it is absorbed rapidly. Some diffusion into the blood may occur after intranasal instillation of penicillin, and small amounts are absorbed from certain other mucous membranes.

Penicillin is therapeutically active when it combines with the albumin fraction of plasma proteins, it is not known whether this

readily into ascitic fluids, where it reaches concentrations comparable to those in the blood. It passes easily from maternal to fetal blood, and detectable quantities are found in the amniotic

distributed in quantities corresponding to the content of extracellular water.

If renal function is normal, 90 to 100 per cent of crystalline penicillin G and its degradation products may be found in the urine within a few hours after a single intramuscular dose. It is important for

excreted in the active, while it Penicillin also is excreted in sweat, milk or

dropsy or impaired renal function, excretion of penicillin is retarded. If renal function is impaired severely, as in patients with anuria, penicillin accumulates in the blood, but the concentration drops rapidly as soon as the anuria is relieved. Acute toxic reactions in man from the accumulation of penicillin in the blood have never been reported.

Because penicillin is excreted rapidly by the kidneys by complete clearance, in a manner similar to that of iodopyracet or aminohippuric acid, numerous attempts have been made to decrease its rate of excretion. Iodopyracet injection, *p*-aminobenzoic acid, *p*-aminohippuric acid and other substances have been used for

this purpose. The most practical compound has been probenecid, which inhibits reversibly a renal tubular transport mechanism by which penicillin is excreted, thus prolonging retention of penicillin in the blood and permitting easier maintenance of therapeutic concentrations in the plasma of the antibiotic. To achieve this effect, probenecid must be given concomitantly with penicillin in small oral doses administered at 6-hour to 8-hour intervals. Drug sensitivity to probenecid has been reported.

Probably the most widely used method for producing sustained concentrations of penicillin in the blood and urine is injection of preparations of small particulate procaine penicillin G. The water-solubility of this salt of penicillin is about 0.7 per cent, and following the intramuscular injection of 300,000 units of suitable water suspension, detectable concentrations of penicillin are found in the blood of most subjects for at least 8 to 12 hours. In tests on human subjects, urine concentrations of penicillin lasted as long as 72 hours after single intramuscular injections of 300,000 units of procaine penicillin. Detectable amounts of penicillin are found in the blood of test subjects for at least 60 hours after the injection of 300,000 units of procaine penicillin suspended in peanut or sesame oil to which 2 per cent aluminum monostearate has been added. Furthermore, preparations of aluminum penicillinate suspended in peanut oil produce the same type of sustained concentrations of penicillin in the blood. Excretion of the antibiotic in the urine continues for a number of days after intramuscular injection of either of the latter two preparations. Physicians should keep in mind that preparations of small particulate crystalline procaine penicillin G are to be used when it seems desirable to prolong a given effective penicillin level. Increased dosage of procaine penicillin in aqueous suspension may increase the magnitude of penicillin concentration as well as prolong the penicillin effect.

Penicillin for Inhalation—Penicillin liquid aerosol or dust may be inhaled through the nose or mouth for application of the drug to the respiratory tract as an adjunct in the treatment of infections encountered in sinusitis, laryngitis, tracheobronchitis, bronchiectasis, bronchial asthma and lung abscess. This route is of value when continued systemic administration is not feasible or when it is desired, in conjunction with systemic therapy, to produce a higher concentration of the drug at the site of infection. Inhalation should not be employed in lieu of adequate systemic therapy for acute infections. In sinus infection it should be employed only when negative pressure can be produced intermittently. Soluble aerosol penicillin produces therapeutic blood levels that may be adequate for the treatment of chronic pulmonary infections susceptible to the drug. Only penicillin mist is suitable for the supportive treatment of lung abscess. Dust penicillin is not recommended for adjunctive inhalation therapy of lung abscess or for the treatment of nasal, pharyngeal or oral infections.

The possibility of sensitivity to penicillin necessitates special caution in the use of inhalation therapy, particularly in patients with asthma or history of allergy. Because of the physical effect of dust, this form of penicillin is more likely to produce broncho-

spasm than is aerosol penicillin. If dust is used, however, particles of 20 to 40 μ are preferable to smaller particles since they have less tendency to cause bronchospasm or to be lost through exhalation. Dust penicillin produces sore throat and other local reactions in the mouth oftener than aerosol penicillin, but its greater convenience for short periods of therapy, particularly in ambulant patients, makes it useful for the management of certain chronic infections. Dust penicillin, because of its tendency to induce bronchospasm, should be employed in infectious asthma only in carefully selected patients, and should not be employed in the presence of pulmonary emphysema or fibrosis.

DOSAGE—As an aerosol, 1 to 2 cc. of a solution containing 25,000 to 50,000 units of penicillin per cubic centimeter may be nebulized and inhaled every 3 to 4 hours. As a dust, 100,000 units are inhaled one to three times daily by means of a suitable device. Inhalation of dust penicillin over a long period increases untoward reactions attributable to contact of the drug with the mucous membranes of the throat and mouth.

Penicillin for Oral or Sublingual Administration.—Penicillin G or O may be administered orally. However, because the drug is inactivated partially by the gastric juice and by certain bacterial enzymes in the lower bowel, it is necessary to use large amounts to achieve significant blood levels. Furthermore, absorption from the gastro-intestinal tract is irregular, hence oral administration requires doses of approximately five times the amount usually recommended for injection. Oral doses should be given between meals, preferably buffered with a suitable antacid such as sodium citrate, dihydroxy aluminum aminoacetate or aluminum hydroxide, although this may be unnecessary with crystalline products prepared in a suitable physical state or with tablets of aluminum penicillin. Soluble penicillin salts also may be added to the milk formulas of infants.

Soluble forms are also suitable for sublingual administration to persons who have difficulty in swallowing tablet forms. However, oral administration of penicillin G or O is recommended only in special instances.

In order to secure effective blood levels of penicillin by the oral route over a more protracted period of time, special esters of penicillin are being utilized or probenecid is administered simultaneously.

DOSAGE—Potassium penicillin G or O or aluminum penicillin may be administered orally (intermittent or continuous infusion). In general the dosage varies with the type of infection, but oral administration should be reserved for less severe

without bacteremia, pneumococcal infections, or minor staphylococcal infections without bacteremia, an initial dose of 500,000 units followed by 100,000 units every 3 hours is recommended.

for 1 or 2 days, or 500,000 units every 6 hours for three doses.

Penicillin for Injection for Prompt Action.—The calcium, potassium or sodium salts of penicillin G and the potassium salt of penicillin O may be dissolved in sterile, pyrogen-free distilled water, isotonic solution of sodium chloride or 5 per cent dextrose solution in concentrations of 10,000 to 100,000 units per cubic centimeter. Injections may be made subcutaneously, intramuscularly or intravenously. The last route is used only for continuous infusion of concentrations of 25 to 50 units per cubic centimeter at the rate of 5,000 to 10,000 units per hour. Because of the rapid excretion of aqueous solutions of penicillin, injections must be repeated every 3 or 4 hours to maintain therapeutic blood levels.

In severe infections, continuous intravenous infusion of a solution containing 25 to 50 units per cubic centimeter should be administered at a uniform rate of 5,000 to 10,000 units per hour. In the penicillin-susceptible infections, with or without bacteremia, the average dosage is 300,000 to 600,000 units per 24-hour period, in chronic pyogenic infections, as an adjunct to surgical treatment, the dosage should be 50,000 to 100,000 units every 6 hours, in acute gonorrhea, 25,000 units may be given to hospitalized patients every 3 hours.

In meningitis, endocarditis and infections complicated by abscess formation or involving serous cavities, parenteral administration should be continued until blood cultures become negative or the acute condition is controlled. Consideration then may be given to the use of other modes of administering penicillin. In the prophylaxis of subacute bacterial endocarditis a minimum of 600,000 units daily should be employed. In the treatment of meningitis,

concentration and amounts indicated above.

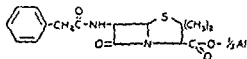
Large single doses of 250,000 units or more of aqueous crystalline penicillin administered intramuscularly once every 12 hours are adequate in uncomplicated pneumococcal pneumonia, but the shorter dosage interval is preferred when less susceptible infections are treated.

Penicillin for Injection for Prolonged Action.—Blood levels of

penicillin G may be prolonged beyond the 3-hour or 4-hour period by various means. Vehicles that delay absorption, such as a mixture of a vegetable oil and 2 per cent aluminum monostearate, allow penicillin to be absorbed slowly from an intramuscular "depot." Various insoluble salts or esters of penicillin G such as procaine in aqueous suspension, vegetable oil or oil and 2 per cent aluminum monostearate now are used chiefly for this purpose. Excretion may be delayed by the simultaneous administration of renal blocking agents such as *p*-aminohippuric acid or probenecid.

Procaine penicillin G in oil may be used in most conditions for which aqueous penicillin solutions are suitable, and are particularly adaptable to the treatment of ambulatory patients or patients who are treated in their homes. A single dose of 300,000 units once every 24 hours usually suffices for ordinary infections caused by penicillin-susceptible organisms. Severe fulminating infections, including bacterial endocarditis, should be treated with doses of 600,000 units given once or twice daily.

ALUMINUM PENICILLIN.—Aluminum penicillin is the trivalent aluminum salt of an antibiotic substance or substances produced by growth of the molds *Penicillium notatum* or *Penicillium chrysogenum*. The structural formula of aluminum penicillin G may be represented as follows:



Physical Properties.—Aluminum penicillin is a light yellow powder having a characteristic odor and taste. The approximate amount that dissolves at 25° in water to give 100 cc. of solution is 0.4 Gm.

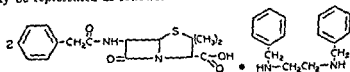
Actions, Uses and Dosage.—See the general statement on penicillin under Penicillin for Oral or Sublingual Administration.

HYNSON, WESTCOTT & DUNNING, INC.

Tablets Aluminum Penicillin: 50,000 units, with sodium benzoate 0.3 Gm.

U. S. patent 2,530,372.

BENZATHINE PENICILLIN G—U.S.P.—Bicillin (WYETH).—Permapen (PFIZER).—*N,N'*-dibenzylethylenediamine dipenicillin G—“Benzathine Penicillin G contains not less than 85 per cent and not less than 1,050 units per mg of total penicillins as benzathine penicillin G. It conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.” *U.S.P.* The structural formula of benzathine penicillin G may be represented as follows.



Physical Properties.—Benzathine penicillin G is a white, odorless, crystalline powder. Its saturated solution is slightly acid or is neutral to litmus, having a pH of 5.5 to 7.5. One gram dissolves in about 2,500 cc. of water and in about 1,000 cc. of alcohol.

Actions and Uses.—Benzathine penicillin G is a complex salt of penicillin. It has relatively low solubility in water and exhibits somewhat more prolonged action than more soluble salts of the

ministered in adequate doses at 6-hour to 8-hour intervals. By the intramuscular route, a single injection produces an effective blood level for 1 to 4 weeks or longer, depending on the size of the dose.

Benzathine penicillin G is indicated for the prevention or treatment of infections susceptible to therapy with penicillin and, in

Following oral administration loose stools have been observed

injection as an aqueous suspension.

every 8 hours. In the acute phase of pneumococcal infections (except meningitis) or in streptococcal pneumonia, an initial injection of 600,000 units of a potassium penicillin G preparation may be supplemented by the oral administration of 200,000 to 300,000 units every 6 to 8 hours, until temperature has remained normal for at least 48 hours. Intramuscular injection of 600,000 units can be used to initiate therapy of pneumococcal and nonhemolytic streptococcal infections without bacteremia, which may be followed by oral administration of 300,000 units every 8 hours. If bacteremia

is present, the oral dose should be increased to 600,000 units or parenteral therapy should be substituted. An injection of 600,000 units every other day should be used in severe infections. In hemolytic streptococcal infections without bacteremia, 200,000 to 300,000 units orally every 6 to 8 hours for at least 7 days is recommended; with bacteremia, an initial injection of 600,000 units should be given, supplemented by oral doses of 200,000 units every 8 hours. In staphylococcal infections without bacteremia, an oral dose of 300,000 units every 6 to 8 hours may be tried, but if ineffective, parenteral therapy should be substituted. When any complication or bacteremia is present in staphylococcal infections, parenteral therapy only should be used. Susceptible staphylococcal infections may be treated with a dose of 1.2 million units, repeated in 48 to 72 hours if required.

Intramuscular injection of a single dose of 600,000 units is recommended as a preventive measure 1 day prior to tonsillectomy, tooth extraction or other minor surgical procedures in patients with a history of rheumatic fever and rheumatic or congenital heart disease. In the prevention of recurrent rheumatic fever, injection of 600,000 units every 2 weeks or 1.2 million units every 4 weeks is recommended. This dosage eliminates the streptococcal carrier state in most persons. In acute beta hemolytic streptococcal infections, a single intramuscular dose of 600,000 units is usually sufficient. In acute gonorrheal urethritis, a single dose of 300,000 units intramuscularly is adequate to effect a cure in most cases. When gonorrheal urethritis is complicated with a suspected primary lesion of

monthly intervals for 3 months. In gonorrheal complications, repeated injections are rarely, if ever, necessary. In gonorrhea complicated by suspected primary syphilis, an injection of 1.2 million units may be expected to eradicate or abort syphilitic infection.

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

Oral Suspension Permaphen: 60 cc. bottles. A suspension containing 60,000 units of benzathine penicillin G in each cubic centimeter. Buffered with sodium citrate. Preserved with 0.016 per cent propylparaben and 0.09 per cent methylparaben.

Aqueous Suspension Permaphen: 1 cc. Steraject cartridges. Each cartridge contains 600,000 units of benzathine penicillin G in each cubic centimeter. Preserved with 0.01 per cent propylparaben and 0.12 per cent methylparaben. Packaged with 10 sterile hypodermic needles.

WYETH LABORATORIES, INC.

Suspension Bicillin (Oral): 60 cc. bottles. A flavored suspension containing 30,000 or 60,000 units of benzathine penicillin G in each cubic centimeter. Buffered with 0.5 per cent sodium citrate and

preserved with 0.12 per cent methylparaben, 0.014 per cent propylparaben and 0.625 per cent sodium benzoate

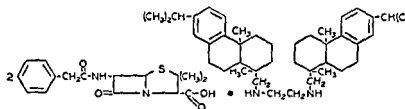
Aqueous Suspension Bicillin (Injection): 1 cc. Tubex cartridges. A suspension containing 600,000 units of benzathine penicillin G in each cartridge. Buffered with 0.5 per cent sodium citrate and preserved with 0.09 per cent methylparaben and 0.01 per cent propylparaben.

10 cc vials A suspension containing 300,000 units of benzathine penicillin G in each cubic centimeter. Buffered with 1 per cent sodium citrate and preserved with 0.12 per cent methylparaben and 0.014 per cent propylparaben.

Tablets Bicillin: 100,000 and 200,000 units

U S patent 2,627,491 U S trademark 569,161.

HYDRABAMINE PENICILLIN G.—Compocillin (ABBOTT).—Hydrabamine penicillin G is a mixture of crystalline penicillin G salts consisting chiefly of the salt of N,N'-bis-(dehydroabietyl) ethylenediamine, with smaller amounts of the salts of the dihydro- and tetrahydro-derivatives. The structural formula of hydrabamine penicillin G may be represented as follows.



Physical Properties.—Hydrabamine penicillin G is a white powder that is practically odorless. It is practically insoluble in water and alcohol and slightly soluble in chloroform.

Actions and Uses.—Hydrabamine penicillin G, a water-insoluble dipenicillin compound salt of a rosin amine base, is useful in the

tions and to patients with a history of rheumatic fever or rheumatic heart disease. As with other penicillin compounds, it is of no value for the treatment or prevention of the common cold or influenza. Given orally, hydrabamine penicillin G promptly produces satisfactory penicillin blood levels when administered in doses of 300,000 to 600,000 units at 6-hour intervals. After 6 hours, the blood level produced by similar single oral doses falls

following oral administration of 600,000 unit doses are approximately twice those obtained with 300,000 unit doses. Animal studies indicate that the hydrabamine base portion of the compound is unabsorbed chiefly when given by the oral route; up to 90 per cent is recovered in the feces with less than 1 per cent found in the urine. Fecal excretion of the base is not influenced significantly by the normal intestinal flora.

Hydrabamine penicillin G has about the same toxicity in animals as benzathine penicillin G. Chronic toxicity studies in animals with doses far in excess of those recommended for human beings have not disclosed hematological or other abnormalities. Clinically, looseness of stools has been observed as a rare side effect and urticaria has been attributed to the drug. Physicians should be alert to the possibility of allergic reactions, stomatitis or monilial infection of the gastro-intestinal tract. As with other penicillin preparations, allergic reactions may be controlled with antihistamine or when there are monilial complications.

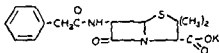
Hydrabamine penicillin G is administered orally for continuous prophylaxis in rheumatic fever, approximately 300,000 units orally once or twice daily is suggested, patients with streptococcal infections who have had rheumatic fever or show signs of rheumatic heart disease should receive a total of 800,000 to 1,200,000 units per day (a smaller amount for children; larger for adults) in four divided doses for the first 5 days, and 600,000 to 750,000 units per day in three divided doses for the second 5 days. The entire 10-day treatment should be administered to such patients even though fever or symptoms disappear before the end of this period.

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ABBOTT LABORATORIES

Oral Suspension Compocillin: 60 cc. bottles. A suspension containing 60,000 units of hydrabamine penicillin G in each cubic centimeter. Preserved with 0.015 per cent propylparaben and 0.135 per cent methylparaben.

POTASSIUM PENICILLIN G—U.S.P.—Benzyl Penicillin Potassium.—Penicillin G Potassium—"Potassium Penicillin G contains not less than .85 per cent of $C_{16}H_{17}KN_2O_4S$ and not less than 90 per cent of total penicillins, calculated as potassium penicillin G." *U.S.P.* The structural formula of potassium penicillin G may be represented as follows:



Physical Properties.—Potassium penicillin G occurs as colorless or white crystals, or as a white to slightly yellow, crystalline

powder. It is odorless or practically so and is moderately hygroscopic. Its solutions are dextrorotatory. It is decomposed by prolonged exposure to temperatures of about 100°, moisture accelerating decomposition. Its solutions deteriorate at room temperature, but solutions stored below 15° remain stable for several days. It is not appreciably affected by air or by light. It is inactivated rapidly by acids and by alkali hydroxides. Its activity is destroyed also by oxidizing agents. Potassium penicillin G is very soluble in water, in saline T S and in dextrose solutions. It is moderately soluble in alcohol but is inactivated by this solvent, by glycerin and by many other alcohols.

Actions and Uses.—Potassium penicillin G is chiefly effective against gram-positive bacteria, particularly against streptococci, pneumococci and clostridial infections but also against gram-

be used for this purpose. However, the convalescent carrier state may be shortened by the concomitant use of adequate amounts of antitoxin and at least 240,000 units of potassium penicillin G per day for not less than 12 days during the active clinical phase of diphtheria. Potassium penicillin G is of little value in mixed infections in which the predominant organism is gram-negative. It is

reaction

Dosage.—See the general statement on penicillin under Penicillin for Inhalation, Penicillin for Oral or Sublingual Administration and Penicillin for Injection for Prompt Action.

ABBOTT LABORATORIES

Potassium Penicillin G—100,000, 200,000, 500,000, 1,000,000 and 5,000,000 unit vials

Dulcet Tablets Potassium Penicillin G (Buffered): 50,000 and 100,000 units. Buffered with calcium carbonate.

U. S. trademark 500,527 (Dulcet).

Tablets Potassium Penicillin G (Buffered): 50,000, 100,000, 200,000, 250,000 and 500,000 units. Buffered with calcium carbonate.

Powdered Potassium Penicillin G: 100,000 units in sifter cartridges for use in Aerohalor.

U. S. trademark 529,568 (Aerohalor).

Soluble Tablets Potassium Penicillin G: 50,000, 100,000 and 250,000 units.

BRYANT PHARMACEUTICAL CORPORATION

Tablets Potassium Penicillin G (Buffered): 50,000, 100,000, 200,000 and 250,000 units. Buffered with calcium carbonate.

Soluble Tablets Potassium Penicillin G: 50,000, 100,000, 200,000 and 250,000 units.

COMMERCIAL SOLVENTS CORPORATION

Potassium Penicillin G: 200,000 and 500,000 units in 20 cc. vials and 1,000,000 units in 50 cc. vials.

Soltabs Potassium Penicillin G: 50,000, 100,000 and 250,000 units.

U. S. trademark 501,394 (Soltabs).

Tablets Potassium Penicillin G (Buffered): 50,000 and 100,000 units. Buffered with glycerides and sodium salts of fatty acids.

R. E. DWIGHT & COMPANY

Potassium Penicillin G: 100,000, 200,000, 500,000 and 1,000,000 unit vials.

THE EVRON COMPANY, INC.

Soluble Tablets Potassium Penicillin G: 50,000, 100,000, 200,000 and 250,000 units.

Tablets Potassium Penicillin G (Buffered): 50,000, 100,000, 200,000 and 250,000 units. Buffered with calcium carbonate.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

Potassium Penicillin G (Buffered): 100,000, 200,000, 500,000, 1,000,000, 2,000,000 and 5,000,000 unit vials. Buffered with 4.5 per cent sodium citrate.

ELI LILLY & COMPANY

Potassium Penicillin G: 100,000, 200,000 and 500,000 units in 5 cc. ampuls and 1,000,000 units in 10 cc. vials.

Tablets Potassium Penicillin G (Buffered): 50,000, 100,000, 200,000, 250,000, 500,000 and 1,000,000 units. Buffered with calcium carbonate.

PARKE, DAVIS & COMPANY

Potassium Penicillin G: Vials of 500,000 and 1,000,000 units

Tablets Potassium Penicillin G (*Buffered*): 50,000 and 100,000 units Buffered with 0.25 Gm. of calcium carbonate.

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

Potassium Penicillin G: 500,000, 1,000,000, 2,000,000 and 5,000,000 unit vials.

Soluble Tablets Potassium Penicillin G: 50,000 and 100,000 units

Tablets Potassium Penicillin G (*Buffered*): 50,000, 100,000, 250,000 and 500,000 units Buffered with calcium carbonate.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Potassium Penicillin G: 500,000 units in 5 cc vials and 1,000,000 units in 20 cc. vials.

Soluble Nebutabs Potassium Penicillin G: 50,000, 100,000, 200,000 and 250,000 units.

Tablets Potassium Penicillin G (*Buffered*): 50,000, 100,000, 200,000, 250,000, 500,000 and 1,000,000 units. Buffered with calcium carbonate

REXALL DRUG COMPANY

Flavored Tablets Potassium Penicillin G (*Buffered*): 50,000 and 100,000 units Buffered with calcium carbonate

SCHENLEY LABORATORIES, INC.

Soluble Tablets Potassium Penicillin G: 50,000 and 100,000 units.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Potassium Penicillin G (*Buffered*): 100,000, 200,000, 500,000, 1,000,000 and 5,000,000 unit vials Buffered with sodium citrate.

Foil-Tabs Potassium Penicillin G (*Buffered*). 50,000, 100,000 and 250,000 units Buffered with 0.34 Gm. of calcium carbonate.

Soluble Foil-Tabs Potassium Penicillin G. 50,000 and 100,000 units

SUCCESS CHEMICAL COMPANY, INC.

Tablets Potassium Penicillin G (*Buffered*). 50,000, 100,000, 200,000 and 250,000 units Buffered with calcium carbonate

Soluble Trit-U-Tabs Potassium Penicillin G: 50,000, 100,000, 200,000 and 250,000 units

THE UPJOHN COMPANY

Potassium Penicillin G: 25 cc. vials. 100,000, 200,000 and 500,000 units in each cubic centimeter.

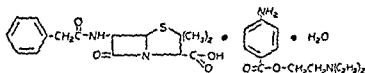
vials of

Tablets Potassium Penicillin G (Buffered): 50,000, 100,000 and 250,000 units. Buffered with 0.25 Gm. calcium carbonate.

WINTHROP-STARNS, INC.

Potassium Penicillin G: 500,000, 1,000,000 and 2,000,000 unit vials.

PROCAINE PENICILLIN G-U.S.P.—Penicillin G Procaine—"Procaine Penicillin G has a potency of not less than 900 U.S.P. Penicillin Units per mg. (89 per cent) It contains not less than 85 per cent of procaine penicillin G. It conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs" U.S.P. The structural formula for procaine penicillin G may be represented as follows:



Physical Properties.—Procaine penicillin G occurs as white or faintly yellow, fine crystals or as a white, very fine, microcrystalline powder. It is odorless or practically so and is not appreciably affected by air or light. Its solutions are dextrorotatory. It is inactivated rapidly by acids, alkali hydroxides and oxidizing agents. One gram dissolves in 250 cc. of water, in about 120 cc. of alcohol and in about 60 cc. of chloroform.

Actions and Uses.—See the general statement on penicillin

Dosage.—See the general statement on penicillin under Penicillin for Injection for Prolonged Action

ABBOTT LABORATORIES

Aqueous Suspension Procaine Penicillin G (Buffered): 1 and 10 cc. vials; 300,000 units in each cubic centimeter. Preserved with 0.135 per cent methylparaben and 0.015 per cent propylparaben Buffered with sodium citrate and citric acid.

Procaine Penicillin G for Aqueous Injection: 1,500,000 unit vials.

Procaine Penicillin G in Oil: 10 cc. vials 300,000 units in each cubic centimeter of sesame oil with 2 per cent aluminum monostearate.

Rapid/Repository Penicillin Aqueous: Buffered Potassium/Procaine Penicillin G: 2 dose (1 cc.) 5 dose (5 cc.) and 10 dose (10 cc.)
one-mpul

BIO-RADSO DRUG COMPANY, INC.

Aqueous Suspension Procaine Penicillin G: 5 and 10 cc. vials. A suspension containing 300,000 units of procaine penicillin G in each cubic centimeter. Preserved with 0.015 per cent butyl *p*-hydroxybenzoate. Buffered with 14 mg. of sodium citrate.

Procaine Penicillin G in Oil: 1 and 10 cc. vials 300,000 units in each cubic centimeter of sesame oil with 2 per cent aluminum monostearate.

Procaine Penicillin G in Oil: 10 cc vials. 300,000 units in each cubic centimeter in peanut oil with 2 per cent aluminum monostearate.

COMMERCIAL SOLVENTS CORPORATION

Procaine Penicillin G (Micronized) in Oil: 10 cc vials. 300,000 units in each cubic centimeter in peanut oil with 2 per cent aluminum monostearate

R. E. DWIGHT AND COMPANY

Aqueous Suspension Procaine Penicillin G with Procaine Hydrochloride 2%: 10 cc. vials A suspension containing 300,000 units of procaine penicillin G and 20 mg of procaine hydrochloride in each cubic centimeter Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

Procaine Penicillin G in Oil. 10 cc. vials. 300,000 units in each cubic centimeter of peanut oil with 2 per cent (w/v) aluminum monostearate

THE W. S. MERRELL COMPANY

Procaine Penicillin G in Oil: 10 cc. vials 300,000 units in each cubic centimeter of sesame oil

PARKE, DAVIS & COMPANY

Procaine Penicillin G in Oil: 10 cc vials 300,000 units in each cubic centimeter of sesame oil with 2 per cent aluminum monostearate.

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

Procaine Penicillin G (Micronized) in Oil: 10 cc vials. A suspension containing 300,000 units in each cubic centimeter of sesame oil with 2 per cent aluminum monostearate.

Aqueous Suspension Procaine Penicillin G with Procaine Hydrochloride 2%: 10 cc vials. A suspension containing 300,000 units of procaine penicillin G and 20 mg of procaine hydrochloride in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

1 cc and 1.67 Steraject cartridges. A suspension containing 600,000 and 1,000,000 units, respectively, of procaine penicillin G in each cubic centimeter Preserved with 0.12 per cent methyl-

paraben and 0.013 per cent propylparaben. Buffered with sodium citrate.

Procaine Penicillin G for Aqueous Injection: Vials of 3,000,000 units. Buffered with 3.8 per cent sodium citrate.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Procaine Penicillin G for Aqueous Injection: Vials of 300,000 and 3,000,000 units.

Procaine Penicillin G (Micronized) in Oil: 10 cc. vials, 300,000 units per cubic centimeter of sesame oil with 2 per cent (w/v) aluminum monostearate.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Procaine Penicillin G (Micronized) in Oil: 10 cc. vials, 300,000 units in each cubic centimeter of sesame oil with 2 per cent aluminum monostearate.

U S patent 2,515,898.

THE UPJOHN COMPANY

Depo-Procaine Penicillin G in Oil: 1 cc. cartridges packaged with disposable cartridge syringe and 10 cc. vials. A suspension in peanut oil containing 300,000 units of crystalline procaine penicillin G with 2 per cent aluminum monostearate.

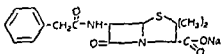
Licensed under U S. patent 2,507,193

THE VITARINE COMPANY, INC.

Aqueous Suspension Procaine Penicillin G with Procaine Hydrochloride 2%: 10 cc vials. A suspension containing 300,000 units of procaine penicillin G and 20 mg of procaine hydrochloride in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

Procaine Penicillin G in Oil. 10 cc vials, 300,000 units in each cubic centimeter of sesame oil with 2 per cent aluminum monostearate.

SODIUM PENICILLIN G—U.S.P.—Benzyl Penicillin Sodium.—Crystalline Penicillin G Sodium.—Penicillin G Sodium.—"Sodium Penicillin G contains not less than 85 per cent of $C_{16}H_{17}N_2NaO_4S$ and not less than 90 per cent of total penicillins, calculated as sodium penicillin G" U.S.P. The structural formula of sodium penicillin G may be represented as follows:



Physical Properties.—Sodium penicillin G is a white to tan powder having a slight characteristic odor. It is very soluble in water.

Actions and Uses.—See the monograph on potassium penicillin G.

Dosage—See the general statement on penicillin under Penicillin for Inhalation, Penicillin for Oral or Sublingual Administration and Penicillin for Injection for Prompt Action

BIO-RAMO DRUG COMPANY, INC.

Sodium Penicillin: 200,000 and 500,000 unit vials.

Sodium Penicillin G (*Buffered*): 200,000, 500,000 and 1,000,000 unit vials

Tablets Sodium Penicillin G (*Buffered*): 50,000 and 100,000 units. Buffered with sodium benzoate

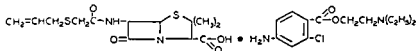
SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Sodium Penicillin G: 200,000 and 500,000 units in 5 cc vials and 1,000,000 units in 20 cc. vials.

E. R. SQUIEB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Powdered Sodium Penicillin G: 100,000 units in Dispulator vials

CHLOROPROCAINE PENICILLIN O—*Depo-Cer-O-Cillin Chloroprocaine* (UPJOHN)—A crystalline salt of 2-chloroprocaine and penicillin O. The structural formula of chloroprocaine penicillin O may be represented as follows.



Physical Properties—Chloroprocaine penicillin O is a white, crystalline powder. It is practically insoluble in water. Chloroprocaine penicillin O is stable at room temperature for a period up to 3 years.

produced by intramuscular injections of an aqueous suspension of chloroprocaine penicillin O are approximately equal to those obtained by a similar penicillin G. With of the antibiotic in as compared with cillin G

As with soluble salts of penicillin O, the majority of patients

sensitive to salts of penicillin G will tolerate chlorprocaine penicillin O without allergic reactions; however, some patients may be sensitive to both penicillin G and penicillin O. In such patients, another antibiotic should be used.

Dosage.—Chlorprocaine penicillin O is administered intramuscularly as an aqueous suspension containing 300,000 units per cubic centimeter. In acute staphylococcic, streptococcic and pneumococcic infections, the minimum dosage is 300,000 units injected once daily and continued until the temperature has returned to normal for at least 48 hours and evidence is present that the infection is disappearing. When these infections are severe, 600,000 units every 12 hours may be employed or replaced by injections of a solution of potassium penicillin O at shorter intervals. In acute gonorrhea, a single injection of 300,000 units is usually sufficient to effect a cure, but patients who fail to respond should be re-treated until a cure has been achieved. In chronic gonorrhea accompanied by complications, higher doses and more prolonged therapy may be required. In the treatment of gonorrhea, the possible masking effect of penicillin on the early signs of syphilis should be kept in mind; appropriate tests should be instituted to confirm or exclude the presence of that disease.

Aqueous suspensions may be kept at room temperature for 3 weeks without a significant loss of potency and without caking. If refrigerated, the suspension should be warmed gradually prior to injection and shaken vigorously to make certain that all of the penicillin is in suspension. Excessive heating should be avoided to prevent destruction of the physical or antibacterial properties of the suspension.

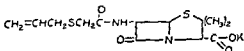
THE UPJOHN COMPANY

Depo-Cer-O-Cillin Chlorprocaine: 1,500,000 unit vials of chlorprocaine penicillin O

U. S. patent 2,647,894 U. S. trademarks 515,760 and 554,422

POTASSIUM PENICILLIN O—Cer-O-Cillin Potassium (Upjohn). Penicillin O is allylmercaptomethyl penicillin, produced biosynthetically by growing the mold in a medium containing allylmercaptoacetic acid.

Penicillin O is assayed in terms of the International Unit defined as the specific penicillin activity contained in 0.6 mcg. of penicillin standard. It is stable in dry form at room temperature for a minimum of 3 years and requires no refrigeration. Solutions may be kept for 3 days under refrigeration without significant loss of potency. The structural formula of potassium penicillin O may be represented as follows:



Physical Properties.—Potassium penicillin O is a white crystalline

powder having an onionlike taste and odor. It is freely soluble in water.

Actions and Uses.—Potassium penicillin O has a spectrum of antibacterial activity similar to that of the soluble salts of penicillin G (see the general statement on penicillin). In experimental animals, penicillin O is found to be less toxic than penicillin G. Absorption and excretion curves of human beings are approximately the same for the two penicillins. Clinically penicillin O has been demonstrated to be as effective as penicillin G and to be less likely to cause sensitivity or allergic reactions. It is particularly useful as a substitute in the treatment of patients sensitive to penicillin G. Physicians should be alert to the development of drug resistant strains. In such instances, therapy should be abandoned.

without the development of allergic phenomena. Some patients may lose their sensitivity to penicillin G during a short course of therapy with penicillin O. If reactions occur that cannot be controlled and they are more serious than the condition under treatment, the drug should be discontinued. When administered orally, penicillin O may produce an onionlike odor of the breath which subsides shortly after the drug is discontinued.

Dosage.—See the general statement on penicillin under Penicillin for Oral or Sublingual Administration and Penicillin for Injection for Prompt Action.

THE UPJOHN COMPANY

Cer-O-Cillin Potassium. 100,000 and 500,000 unit vials.

Tablets Cer-O-Cillin Potassium (Buffered): 100,000 units. Buffered with 0.25 Gm. calcium carbonate.

Polymyxin

Polymyxin is the generic term employed to designate a series of related antibiotics derived from various strains of the spore-forming soil bacterium, *Bacillus polymyxa* (*B. aerosporus* Greer). The various polymyxins that have been isolated are differentiated by affixing letters of the alphabet which do not necessarily signify the order of isolation. Polymyxin B is the least toxic of those adequately studied. Chemically, the polymyxins are basic polypeptides. Polymyxin B contains leucine, threonine, phenylalanine, α,γ -diaminobutyric acid and a fatty acid of empirical formula, $C_{18}H_{35}NO_2$. It is stable in solution and stable to gram-negative micro-organisms. See the monograph on polymyxin B sulfate.

OXYTETRACYCLINE-POLYMYXIN B—See the monograph in the section on antibiotic mixtures.

POLYMYXIN B SULFATE-U.S.P.—Aerosporin Sulfate (BURROUGHS WELLCOME).—"Polymyxin B Sulfate is an antibacterial substance produced by the growth of *Bacillus polymyxa*. It has a potency of not less than 6,000 U.S.P. Polymyxin B Units per mg, calculated on the dried basis." U.S.P.

Physical Properties.—Polymyxin B sulfate is a white to cream-colored irregular scalelike material, which has no definite melting point, but decomposes at about 230°. It is soluble in water and isotonic sodium chloride solution. A 2 per cent solution has a pfl of about 5.7.

Actions and Uses.—Polymyxin B sulfate, an antibiotic derived from an isolated strain of *Bacillus polymyxa*, is bactericidal in vitro for most gram-negative micro-organisms *Escherichia coli*, *Shigella*,

Most strains of *P. aeruginosa* are highly sensitive. Clinical observations indicate that the development of bacterial resistance is unlikely.

Polymyxin B sulfate is effective clinically by intramuscular injection (and intrathecally, when indicated) for the treatment of

urinary tract
other gram-
li, *K. pneu-*
tive to poly-
he antibiotic
en intramus-

cularly, the drug should be given intrathecally as well as intramuscularly for the treatment of susceptible meningeal infections. The intrathecal doses required do not produce systemic toxic effects and the drug is considered relatively nonirritating to the meninges. Intrathecal injections should be made with the care that is essential in the performance of repeated spinal punctures.

Polymyxin B sulfate, when given parenterally, may produce neurotoxic and/or nephrotoxic effects, but it has a low degree of toxicity when used in doses below 3 mg. per kilogram of body weight per day. Neurologic disturbances usually are subjective and include dizziness, mild weakness and paresthesias of the mouth, face, and, less frequently, of the extremities. Usually, these are not considered sufficiently serious to warrant discontinuance of therapy. Nephrotoxic effects, with damage to the kidney tubular epithelium, are manifested by albuminuria and nitrogen retention. The danger of renal damage is minimal when the drug is administered within the recommended dosage range. Other toxic effects include occasional drug fever and pain at the site of injection which can be lessened in the de-

under close observation where there is access to adequate laboratory facilities. Renal dysfunction and nitrogen retention do not contraindicate injection of the drug when it is specifically indicated unless such use is found to aggravate pre-existing renal damage.

Polymyxin B sulfate also may be useful orally in the nonsystemic treatment of certain intestinal infections such as *Shigella* or *Pseudomonas enteritis*, when present as a pathogen. It is too poorly absorbed orally to warrant use by this route in the treatment of systemic infections. Toxic manifestations have not been observed with oral use of the drug.

Polymyxin B sulfate also is useful by topical application for the treatment of local infections caused by susceptible gram-negative bacilli, especially *Pseudomonas aeruginosa*. It may be employed locally also to prevent contamination by gram-negative organisms of wounds or burns.

An ophthalmic ointment containing 20,000 units per gram also may be employed for the treatment and preoperative prophylaxis of eye infections, but it should not be used alone in ocular infections that involve deep structures of the eye or in those infections that may become systemic.

Dosage.—Intramuscularly, the average daily dosage extends from 1.5 mg. (15,000 units) to 2.5 mg. (25,000 units) per kilogram of body weight. The total daily dosage should not exceed 2.5 mg. per

within 30 minutes to 2 hours after injection, one-half the peak level is present after 6 hours, with detectable levels up to 12

chloride solution to 50 mg. of the drug. Solutions prepared for intramuscular use and containing procaine should not be used for

and mixed with a suitable food or dissolved in water and flavored as desired.

For topical application, the drug, in sterile dry form, is dissolved in distilled water or isotonic sodium chloride solution for admin-

istration as drops, spray, wet dressing or irrigation. Concentrations of 0.1 per cent (10,000 units per cubic centimeter) to 0.25 per cent (25,000 units per cubic centimeter) are considered to be effective and nonirritating. Concentrations of 1 per cent or more may produce local irritation when applied to sensitive areas such as the eye. Neither bacterial resistance nor sensitivity reactions have been observed, but until further experience is gained, a total of not more than 2,000,000 units daily should be applied in cases of severe burns and open wounds. Solutions of the antibiotic are stable for at least 6 months if kept under refrigeration.

A small quantity of ophthalmic ointment is placed in the conjunctival sac, three or four times daily, for the treatment of superficial, susceptible infections, as a preoperative prophylactic, it is applied to both eyes on the day prior to surgery.

BURROUGHS WELLCOME & COMPANY, INC.

Aerosporin Sulfate (Parenteral): 500,000 unit vials. Each vial contains 500,000 units of polymyxin B sulfate equivalent to 50 mg of polymyxin B standard

Sterile Powder Aerosporin Sulfate (Topical): 200,000 unit vials. Each vial contains 200,000 units of polymyxin B sulfate equivalent to 20 mg of polymyxin B standard.

Tablets Aerosporin Sulfate: 500,000 units. Each tablet contains 500,000 units of polymyxin B sulfate equivalent to 50 mg. of polymyxin B standard

U S patent 2,565,057 U S trademark 505,252

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

Ointment Polymyxin B Sulfate: 14.2 Gm tubes. An ointment containing 20,000 units of polymyxin B as the sulfate in each gram

Ophthalmic Ointment Polymyxin B Sulfate: 3.5 Gm tubes. An ointment containing 20,000 units of polymyxin B as the sulfate in each gram.

Sterile Powder Polymyxin B Sulfate (Parenteral): 500,000 unit vials. Each vial contains 500,000 units of polymyxin B sulfate equivalent to 50 mg. of polymyxin B standard.

Sterile Powder Polymyxin B Sulfate (Topical): 200,000 unit vials. Each vial contains 200,000 units of polymyxin B sulfate equivalent to 20 mg. of polymyxin B standard

Soluble Tablets Polymyxin B Sulfate: 250,000 units of polymyxin B as the sulfate.

Streptomycin and Dihydrostreptomycin

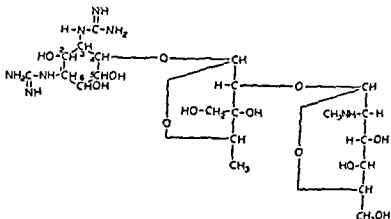
Streptomycin is a basic organic compound of moderate molecu-

When streptomycin is administered by mouth, practically none is absorbed and the bulk of the dose is excreted in the stool. The same is true when streptomycin aerosols are inhaled. For this reason streptomycin must be administered parenterally for the treatment of systemic infections. Maximal concentrations in the blood occur at the end of intravenous injections. Following intramuscular injection, there is a gradual rise, peak levels of streptomycin being found in the blood in 1 to 2 hours. While there is some evidence that the blood concentrations of streptomycin are maintained longer after intramuscular injection, the levels may fall so rapidly that only small amounts of streptomycin are found in the blood 4 hours after intramuscular injection of a therapeutic dose. The concentration and persistence of streptomycin in the blood are related to the size of the dose injected but are not proportional to it.

Excretion by the kidneys is greatest in the 2 hours following intramuscular or intravenous injection of streptomycin; 30 to 60 per cent may be excreted in the urine within 12 hours if renal function is normal, and the bulk is excreted within 24 hours. A small amount is excreted in the bile and eliminated in the stool. Small quantities of this antibiotic are excreted in milk, saliva, sweat and tears. When renal function is impaired seriously, the rate of excretion of streptomycin is decreased and the drug accumulates in the blood. Since this may result in a toxic effect, particular caution should be observed in patients receiving unusually large dosage and in those with impaired renal function that may result in unduly high blood levels. The toxicity of streptomycin and dihydrostreptomycin is negligible for most short-term therapy although allergic reactions tend to occur more frequently with streptomycin. In some patients, prolonged therapy with streptomycin may cause disturbances of vestibular function. It is less likely than dihydrostreptomycin to cause disturbances of auditory function. Conversely, in these patients, dihydrostreptomycin is less likely than streptomycin to cause disturbance of vestibular function but more apt than streptomycin to produce tinnitus and impairment of hearing.

Streptomycin does not pass readily into red blood cells, and it apparently does not pass into the pus in abscesses. The antibiotic is distributed only in the extracellular water of the body. It diffuses so slowly into the spinal fluid that in many instances it may not be detectable, despite repeated parenteral injections. On the other hand, it has been reported to occur in easily detectable amounts in the spinal fluid of patients with frank meningitis. This antibiotic passes over slowly into pleural, synovial and pericardial effusions and, when present, concentrations almost always are considerably lower than those in the blood. Streptomycin passes easily into normal peritoneal fluid or into the exudate of a peritonitis, and it is found in ascitic fluid, generally in concentrations lower

DIHYDROSTREPTOMYCIN SULFATE-U.S.P.—"Dihydrostreptomycin Sulfate contains an amount of $(C_{21}H_{41}N_7O_{12}) \cdot 3H_2SO_4$, equivalent to not less than 65 per cent of dihydrostreptomycin (the antibiotic activity of 650 mcg. of the base in each mg.), except that if it is crystalline Dihydrostreptomycin Sulfate, it contains the equivalent of not less than 65 per cent of the antibiotic activity per mg.). Dihydrostreptomycin Sulfate conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs." *U.S.P.* The structural formula of the free dihydrostreptomycin base may be represented as follows



Physical Properties.—Dihydrostreptomycin sulfate occurs as white or faintly yellow granules or as a white powder. It is nearly odorless and has a slightly bitter taste. It is not affected by air or light and does not deliquesce.

Actions and Uses.—See the monograph on streptomycin sulfate

Dosage.—Dihydrostreptomycin sulfate is administered in doses similar to those of streptomycin. Unlike streptomycin, dihydrostreptomycin sulfate must be injected by the intramuscular route only. *It must not be injected intravenously.* Dihydrostreptomycin sulfate is not recommended for use in meningeal tuberculosis. Ordinarily, it should not be injected intrathecally. Administration by this route has been shown to increase the likelihood of ototoxic manifestations, varying from mild impairment to total loss of hearing. When intrathecal therapy is deemed necessary, streptomycin sulfate is the drug of choice, although its use is not entirely free from similar hazards. However, when a seriously ill patient, known to be allergic to streptomycin, is considered to be in need of intrathecal treatment, dihydrostreptomycin sulfate may be employed. In such instances, the procedure is as follows: Dissolve the intrathecal dose (25 mg. per day or 50 mg. every other day, but never more than 1 mg. per kilogram of body weight) in 10 cc. of water for injection-U.S.P. or spinal fluid. After first withdrawing a slightly greater volume of spinal fluid, inject the solution

slowly over a period of at least 10 minutes. Intraspinal therapy rarely is indicated except in tuberculous meningitis.

Intramuscular injection of the drug may cause pain, which may be reduced by observance of the following suggestions: (a) allow 12-hour intervals between injections; (b) use only fresh solutions; (c) restrict maximum volume of injection at any one site to 2 cc.,

contributes approximately 0.3 cc. to the volume of solution made

ABBOTT LABORATORIES

Dihydrostreptomycin Sulfate: Vials of dihydrostreptomycin sulfate powder, containing the equivalent in activity to 1 Gm. or 5 Gm. of dihydrostreptomycin base

Solution Dihydrostreptomycin Sulfate: 2 cc. vial A solution containing dihydrostreptomycin sulfate equivalent in activity to 0.5 Gm. of dihydrostreptomycin base in each cubic centimeter. Preserved with 0.9 per cent benzyl alcohol and 0.1 per cent sodium metabisulfite.

BIO-RAMO DRUG COMPANY, INC.

Dihydrostreptomycin Sulfate: Vials of dihydrostreptomycin sulfate powder, containing the equivalent in activity to 1 Gm. or 5 Gm. of dihydrostreptomycin base

ELI LILLY & COMPANY

Dihydrostreptomycin Sulfate. 5 and 20 cc ampuls Dihydrostreptomycin sulfate powder equivalent in activity to 1 and 5 Gm., respectively, of dihydrostreptomycin base

Solution Dihydrostreptomycin Sulfate: 2 cc. ampuls and 10 cc. vials. A solution containing dihydrostreptomycin sulfate equivalent in activity to 0.5 Gm. of dihydrostreptomycin base in each cubic centimeter. Preserved with 0.25 per cent phenol.

THE WM S MERRELL COMPANY

Dihydrostreptomycin Sulfate: 5 and 20 cc. vials Dihydrostreptomycin sulfate powder equivalent in activity to 1 and 5 Gm., respectively, of dihydrostreptomycin base.

PFIZER LABORATORIES, DIVISION OF CHAS PFIZER & COMPANY, INC.

Dihydrostreptomycin Sulfate: 20 cc. vials. Dihydrostreptomycin sulfate powder equivalent in activity to 1 or 5 Gm. of dihydrostreptomycin base

Solution Dihydrostreptomycin Sulfate: 2.5 cc. Steraject cartridges, 2.5 and 12.5 cc. vials A citrate buffered solution containing the

equivalent of 0.4 Gm. of dihydrostreptomycin base in each cubic centimeter. Stabilized with 1 per cent sodium bisulfite and preserved with 0.25 per cent phenol.

PREMO PHARMACEUTICAL PRODUCTS, INC.

Dihydrostreptomycin Sulfate: 5 and 20 cc. vials. Dihydrostreptomycin sulfate powder equivalent in activity to 1 and 5 Gm., respectively, of dihydrostreptomycin base.

SHARP & DOHME, DIVISION OF MERCK & Co., INC.

Dihydrostreptomycin Sulfate: 5 and 20 cc. vials. Dihydrostreptomycin sulfate powder equivalent in activity to 1 and 5 Gm., respectively, of dihydrostreptomycin base.

Solution Dihydrostreptomycin Sulfate: 2 and 10 cc. vials. A solution containing dihydrostreptomycin sulfate equivalent in activity to 1 and 5 Gm. of dihydrostreptomycin base, respectively. Buffered with sodium citrate. Preserved with 0.2 per cent sodium bisulfite.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Dihydrostreptomycin Sulfate: 5 and 20 cc. vials. Dihydrostreptomycin sulfate powder equivalent in activity to 1 and 5 Gm., respectively, of dihydrostreptomycin base.

U S patent 2,498,574

THE UPJOHN COMPANY

Dihydrostreptomycin Sulfate: 5 and 20 cc. vials. Dihydrostreptomycin powder equivalent in activity to 1 and 5 Gm., respectively, of dihydrostreptomycin base.

Solution Dihydrostreptomycin Sulfate: 2 and 10 cc. vials. A solution containing dihydrostreptomycin sulfate equivalent in activity to 0.5 Gm. of dihydrostreptomycin base in each cubic centimeter. Preserved with 0.25 per cent phenol.

STREPTOMYCIN CALCIUM CHLORIDE.—Streptomycin calcium chloride is a double salt of streptomycin in which the composition is a streptomycin trihydrochloride calcium chloride complex. For base see the mono-

chloride complex is
very soluble in water
the unopened con-

tainer for a period up to 1 year

Actions, Uses and Dosage.—See the monograph on streptomycin sulfate.

BIO-RAMMO DRUG COMPANY, INC.

Streptomycin Calcium Chloride Complex: Vials of streptomycin calcium chloride complex equivalent in activity to 1 Gm. of streptomycin base.

SHARP & DOHME, DIVISION OF MERCK & CO., INC.

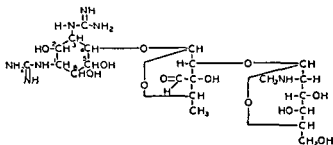
Streptomycin Calcium Chloride Complex: 5 and 20 cc vials. Streptomycin calcium chloride complex equivalent in activity to 1 and 5 Gm. of streptomycin base, respectively

U. S. patent 2,446,102

STREPTOMYCIN SULFATE-U.S.P.—"Streptomycin Sulfate contains an amount less than 65 per cent of Streptomycin Sulfate and Drug Adm drugs" *U.S.P.*

Streptomycin is marketed as a sterile powder in airtight ampuls or vials. Its potency is not less than 300 mcg per milligram. At least two forms, designated A and B, have been isolated so far. Streptomycin in dry form may be stored at room temperature, not exceeding 30°, for periods up to 2 years; however, it should be stored in the original unopened container to prevent contamination.

danger of contamination. The structural formula of the free streptomycin base may be represented as follows:



Physical Properties.—In salt form, streptomycin occurs as white to slightly pink or pale-brown granules or powder. It has a slightly bitter taste and is odorless, or nearly so. It is hygroscopic and may deliquesce on exposure to air. It is very soluble in water but

two antibiotics became widespread, the emergence of strains of pathogenic bacteria, which were resistant to the antibacterial effects of these antibiotics, was increasingly noted. As has been pointed out previously, the majority of strains of certain of the gram-negative pathogens, such as *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Aerobacter aerogenes*, now being isolated from infectious processes, are resistant to these antibiotics. The same is true for strains of *Streptococcus fecalis*. For these reasons, the use of streptomycin or dihydrostreptomycin should be limited to the treatment of infections produced by bacteria that have been shown by laboratory tests to be susceptible to the antibacterial effects of these two antibiotics. In fact, a number of authorities in this field now recommend that streptomycin or dihydrostreptomycin be used only in the treatment of suitable cases of tuberculosis, except in those special instances of infection proved to be susceptible to these antibiotics.

Both streptomycin and dihydrostreptomycin may produce toxic effects such as drug fever, dermatitis or other allergic manifestations. The most serious toxic effects produced by either are those involving the eighth nerve. Permanent and grave damage marked by severe vertigo and/or loss of hearing may occur. Because of these possibilities, careful and accurate auditory and vestibular function tests

or streptomycin should be discontinued within a few days if such symptoms have been observed.

Persons who are frequently in contact with these antibiotics, such as pharmacists, nurses or attendants who administer them, or attendants in central supply rooms where syringes used for the administration of these antibiotics are cleaned, may develop contact dermatitis. For this reason, they should protect themselves by wearing rubber gloves, masks and spectacles when in contact with these antibiotics.

Dosage.—For intramuscular injection, the powder should be dissolved in sterile, pyrogen-free distilled water or isotonic solution of sodium chloride to give a concentration of 100 to 200 mg. of streptomycin base per cubic centimeter. For subcutaneous injection, more dilute solutions are recommended. If the drug is administered by intravenous drip, 1 to 2 Gm. dissolved in a liter of isotonic solution of about 1 to 20 mg. per liter should be given. For intrathecal injection, 50 mg. per 50 mg. per

The dosage of streptomycin should be governed by the susceptibility of the organism responsible for the infection. In severe fulminating infections, doses of 2 to 4 Gm. daily may be necessary, given parenterally in divided doses every 6 hours. In less severe infections, and with highly susceptible organisms, daily doses of

and meningeal forms, doses of 1 Gm of streptomycin are given intramuscularly two or three times weekly in conjunction with aminosalicylic acid for a total of 120 days. In acute miliary tuberculosis and tuberculous meningitis, intramuscular doses of 2 Gm, or more daily are given. In tuberculous meningitis, the intrathecal injection of 50 mg of streptomycin every 1 or 2 days may be used in conjunction with the intramuscular administration of streptomycin.

For inhalation therapy with an aerosol of streptomycin, the sulfate is dissolved in distilled water to make a solution containing the equivalent of 50 to 100 mg of the base in each cubic centimeter. Nebulization of an amount (1 or 2 cc.) sufficient to provide inhalation of 100 mg. five or six times daily every 3 hours is recom-

or opalescence

It is important to give sufficiently large doses to inhibit or kill the infecting organisms quickly, since the development of "fastness" to streptomycin is common and may occur rapidly. Inadequate dosage predisposes to the development of resistant strains of the organisms

ABBOTT LABORATORIES

Streptomycin Sulfate: 6 cc vials. Vials of streptomycin sulfate equivalent in activity to 1 Gm of streptomycin base.

THE WM S. MERRELL COMPANY

Streptomycin Sulfate: 5 and 20 cc vials. Streptomycin sulfate equivalent in activity to 1 and 5 Gm of streptomycin base, respectively.

PFIZER LABORATORIES, DIVISION OF CHAS PFIZER & COMPANY, INC.

Streptomycin Sulfate. 20 cc. vials. Streptomycin sulfate equivalent in activity to 1 or 5 Gm. of streptomycin base.

Solution Streptomycin Sulfate: 25 cc. Steraject cartridges, 2.5 and 12.5 cc vials. A citrate buffered solution containing the equivalent of 0.4 Gm of streptomycin base in each cubic centimeter. Stabilized with 0.2 per cent sodium bisulfite and preserved with 0.25 per cent phenol.

E R SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Streptomycin Sulfate. 5 and 20 cc vials. Streptomycin sulfate equivalent in activity to 1 and 5 Gm, respectively, of streptomycin base.

U S patent 2,449,866

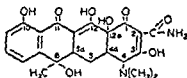
THE UPJOHN COMPANY

Streptomycin Sulfate: 30 cc. vials. Streptomycin sulfate equivalent in activity to 1 Gm of streptomycin base.

STREPTODUOCIN.—See the monograph in the section on antibiotic mixtures.

Tetracycline

TETRACYCLINE-U.S.P.—Tetracyn (PFIZER).—4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide—"Tetracycline contains in each mg the antibiotic activity of 975 mcg. of $C_{22}H_{24}N_2O_8$, calculated on the anhydrous basis. May contain up to 6 molecules of water. Tetracycline conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs" *U.S.P.* The structural formula of tetracycline may be represented as follows.



Physical Properties.—Tetracycline is a yellow, odorless, crystalline powder. It is stable in air, but exposure to strong sunlight causes it to darken. Its potency is affected in solutions of pH below 2, and is destroyed rapidly by alkali hydroxide solutions. One gram of tetracycline dissolves in about 2,500 cc. of water and in about 50 cc. of alcohol. It dissolves readily in dilute hydrochloric acid and in alkali hydroxide solutions. It is practically insoluble in chloroform and in ether. The pH of a saturated solution is between 3.0 and 7.0.

Actions and Uses.—Tetracycline is an antibiotic isolated from the elaboration products of certain *Streptomyces* species when the organism is grown on suitable culture media. It is prepared also by the catalytic halogenation of chlortetracycline (Aureomycin) or oxytetracycline (Terramycin). It differs from the former only in the replacement of the chlorine atom in the structure by a hydrogen atom and from the latter only in the replacement of one hydroxyl group by a hydrogen atom. Tetracycline, the base, has the same actions and uses as tetracycline hydrochloride. (See the monograph on tetracycline hydrochloride.)

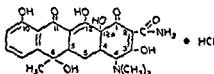
Dosage.—Tetracycline is administered orally. The dosage is the same as for the hydrochloride, which also is expressed in terms of the base.

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

Oral Suspension Tetracyn: 15 Gm. vials. A powder with added flavoring for suspension in distilled water to give a solution containing 25 mg. of tetracycline in each cubic centimeter.

Pediatric Drops Tetracyn: 1 Gm. bottles. A powder with added flavoring to be suspended with water to give a preparation containing 100 mg. of tetracycline in each cubic centimeter.

TETRACYCLINE HYDROCHLORIDE-U.S.P.—Achromycin Hydrochloride (LEDERLE).—Tetracyn Hydrochloride (PFIZER)—4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydrochloride than 90 per de conforms ministration concerning certification of antibiotic drugs" U.S.P. The structural formula of tetracycline hydrochloride may be represented as follows



Physical Properties—Tetracycline hydrochloride is a yellow, odorless, crystalline powder. It is stable in air, but exposure to strong sunlight in moist air causes it to darken. Its potency is affected in solutions of pH below 2 and is slowly destroyed by alkali hydroxide solutions. Its 1 in 100 solution has a pH of about 2.5. One gram dissolves in 10 cc of water and in about 100 cc of alcohol, the aqueous solution becoming turbid after some time because of hydrolysis. It is soluble in solutions of alkali hydroxides and carbonates and is practically insoluble in chloroform and in ether.

Actions and Uses.—Tetracycline hydrochloride has actions and uses similar to those of chlortetracycline and oxytetracycline. Clinical evidence indicates that it is useful in the treatment of infections produced by bacteria that have been noted to be susceptible to the antibacterial effects of either of those antibiotics. Information relative to antiviral action is currently lacking as is also knowledge concerning its effect upon Rickettsiae. No antifungal activity has been demonstrated for tetracycline. An important finding is that if micro-organisms are resistant to chlortetracycline or oxytetracycline, they tend to be resistant to tetracycline also, however, clinical studies have shown that tetracycline may be effective after treatment with chlortetracycline or oxytetracycline has proved ineffective.

Tetracycline has the same range of experimental toxicity both

blood-brain barrier more easily, so that higher concentrations of this compound have been found in the spinal fluid than of either of the other two agents. Tetracycline is excreted in the urine and in

and partial loss of hearing. Skin eruptions frequently may be controlled with antihistamine drugs. Audiometric testing should be done prior to and at regular intervals during treatment to detect any hearing impairment that may occur. It has not been determined whether or not auditory impairment is permanent. Disturbances in the serum electrolyte pattern may be alleviated readily by the administration of supplemental potassium chloride. The aforementioned toxic reactions are unlikely to occur with any degree of frequency or severity when recommended dosages are administered.

Dosage.—Viomycin sulfate is administered by intramuscular injection, preferably into the gluteal, thigh or deltoid muscles. It is important to rotate the site of injection with each dose, and injection should be made slowly. Dosage is expressed in terms of the equivalent weight of viomycin base. The drug is diluted with either water for injection or isotonic sodium chloride solution to make concentrations not exceeding 0.5 Gm. per cubic centimeter. In the dry form it may be stored at room temperature for 24 months without appreciable loss of potency. Solutions may be stored at room temperature under sterile conditions for 1 week without significant loss of potency, but it is recommended that they be stored in a refrigerator.

For most forms of tuberculosis, an intramuscular dose of 2 Gm. (given in two doses of 1 Gm. each, 12 hours apart) every third day is recommended, either alone or in conjunction with aminosalicylic acid (12 Gm. daily by the oral route). At this dosage, therapy should be continued for at least 4 to 6 months, dependent on the response of the lesion. In special instances, a daily dosage not to exceed 2 Gm. (in divided doses) for a period of not more than 1 month may be administered if facilities are available for repeated measurement of serum electrolytes, renal and hepatic function and audiometric changes. In the presence of impaired renal function, the dosage should be much less than 2 Gm. every third day, with very close observation of the patient for toxic manifestations. When the total daily dosage is more than 1 Gm., it must be administered in two equal divided doses separated by a 12-hour interval.

CIBA PHARMACEUTICAL PRODUCTS, INC.

Powder Vinactane Sulfate: Vials containing the equivalent of 1 Gm. of viomycin as the sulfate.

U. S. patent 2,633,445.

PRIZER LABORATORIES, DIVISION OF CHAS. PRIZER & COMPANY, INC.

Powder Viocin Sulfate: Vials containing the equivalent of 1 Gm. of viomycin as the sulfate.

ANTIBIOTIC MIXTURES

BACITRACIN-NEOMYCIN.—Bacimycin (WALKER).—A mixture of bacitracin and neomycin sulfate.

Action and Uses.—Bacitracin-neomycin provides a wider spec-

trum of antibacterial action than can be achieved when either of these antibiotics is employed singly. Since the action of the components is merely additive, they should be combined in the proportion of the concentrations usually considered effective when either is used alone. The combination is useful only for topical application in treating mixed pyogenic surface infections when it is usually impracticable to obtain laboratory studies to identify the infecting micro-organisms or their susceptibility to chemotherapeutic agents. The mixture is effective in the treatment of impetigo contagiosa, impetiginized dermatitis, ecthyma, paronychia, furunculosis, pustular folliculitis, cutaneous ulcers, impetiginized atopic dermatitis, secondarily infected second and third degree burns, infectious eczematoid dermatitis and in seborrheic dermatitis or other cutaneous lesions which are either produced or complicated by pyogenic infection susceptible to either or both bacitracin and neomycin. The mixture is not recommended for prophylactic use because of a lack of satisfactory evidence to indicate its effectiveness for that purpose.

Since the antibiotic components of bacitracin-neomycin rarely produce sensitization when applied topically, such use is considered unlikely to hamper their occasional systemic employment singly when either may be indicated. In the treatment of susceptible infections, patients should be alert to the possibility of allergic reactions, particularly in the case of the mixture should they be sensitive to either component or to the vehicle. Constant observation also is necessary to detect overgrowth of nonsusceptible organisms as a possible complication of prolonged application.

Dosage.—Bacitracin-neomycin is applied topically in the form of an ointment containing 500 units of bacitracin and 5 mg. of neomycin sulfate per gram. In the treatment of dermatological infections, the ointment is applied two to five times daily to the affected areas. Well-established dermatological procedures, including good skin hygiene and local debridement, whenever necessary, should be followed in conjunction with topical antibiotic therapy.

WALKER LABORATORIES, INC.

Ointment Bacimycin: 14.2 Gm. tubes. An ointment containing 500 units of bacitracin and 5 mg. of neomycin sulfate in each gram.

Oxytetracycline-polymyxin B.—Oxytetracycline Hydrochloride is a tetracycline antibiotic. The structural formula for the monograph on polymyxin B sulfate is not known.

Actions and Uses.—Oxytetracycline-polymyxin B is useful for ophthalmic application in the prevention and treatment of pyogenic mixed surface infections of the eye that are likely to be susceptible to either or both of these antibiotics. Because poly-

myxin B is considered the antibiotic of choice against pseudomonal infections, its use in fixed combination with a broad spectrum antibiotic may be justified on the basis that the incidence of ocular infections complicated by the presence of *Pseudomonas aeruginosa* apparently is increasing. The particular effectiveness of polymyxin B against gram-negative bacteria enhances the action of oxytetracycline against both gram-p- While synergism rarely may of infection, the actions of t primarily additive; therefore to the usual concentrations in which each is employed singly.

Oxytetracycline-polymyxin B is considered effective in the treatment of acute and subacute purulent conjunctivitis, acute catarrhal conjunctivitis and chronic blepharoconjunctivitis not involving the meibomian gland, the mixture also is effective as a prophylactic prior to ocular surgery. It may be useful in the management of infection complicating a corneal ulcer, epiphora secondary to conjunctival infection and acute trachoma. The mixture should r to the uveitis, retinitis and other deep-seated infections, it should be supplemented by systemic antibiotic or other therapy that is indicated.

Oxytetracycline-polymyxin B usually is well tolerated by the membranes of the eye. Allergic reactions may be encountered, but these are rare. If severe reactions occur, the mixture should be discontinued. When sensitization to only one component occurs, therapy with the other alone may be continued if the infection is susceptible to it. Bacterial resistance to either antibiotic component ordinarily does not develop, even under continuous therapy.

Dosage.—Oxytetracycline-polymyxin B is applied only topically to the eye as an ophthalmic ointment containing the equivalent of 5 mg. of oxytetracycline base and 10,000 units of polymyxin B base per gram. For the treatment of surface ocular infections, a small quantity of such ointment is applied to each affected eye four to six times daily; for prophylaxis in operative procedures, a small quantity is placed in both eyes several times during the day preceding surgery and into the operated eye at the time of each dressing. In blepharitis, scales and crusts should be removed and the ointment applied over the lid margin. Treatment lasting from 10 to 14 days usually is sufficient for acute infections; in chronic cases, treatment may be required up to 3 months. Careful clinical follow-up is advisable. If infection persists, a second course or change of treatment should be instituted.

PRIZER LABORATORIES, DIVISION OF CHAS. PRIZER & COMPANY, INC.

Ophthalmic Ointment Terramycin Hydrochloride with Polymyxin B Sulfate: 3.54 Gm. tubes. An ointment containing 5 mg. of oxytetra-

cycline as the hydrochloride and 10,000 units of polymyxin B as the sulfate (equivalent to 1 mg. of polymyxin B sulfate) in each gram.

U. S. patent 2,516,080. U. S. trademark 577,504.

STREPTODUOCIN—STREPTODUOCIN FOR INJECTION.—U.S.P.—Combistrep (PFIZER)—Distreptocin (LILLY).—Dihydrostreptomycin-Streptomycin for Injection—"Streptoduocin for Injection is a sterile mixture of approximately equal parts of dihydrostreptomycin sulfate and streptomycin sulfate. It contains not less than 90 per cent of the labeled amount of streptoduocin, of which amount not less than 45 per cent and not more than 55 per cent is streptomycin base. Streptoduocin for Injection conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs." *U.S.P.* For the structural formula for the individual components, see the monographs on streptomycin sulfate and dihydrostreptomycin sulfate.

Physical Properties.—Streptoduocin is a white to pale cream-colored powder. It is odorless or has only a faint odor. It is hygroscopic but is stable in air and in light.

Actions and Uses.—Streptoduocin, a mixture of equal parts of streptomycin and dihydrostreptomycin sulfates, has the same actions and uses as its individual components. (See the mono-

each of the components. The total dosage of the mixture in terms of streptomycin base, therefore, should not exceed the recommended dose for either of the components when used singly. Likewise, as with the separate employment of the components, pre-existing renal impairment interferes with excretion, producing high blood levels and increasing the risk of toxicity. When such impairment is present, the dosage should be reduced to allow for drug retention, and the plasma blood level should not exceed 20 to 25 mcg per cubic centimeter of streptomycin base. The mixture cannot be used in patients sensitive to either streptomycin or dihydrostreptomycin. It also may sensitize patients to both components simultaneously. Streptoduocin is indicated in the treatment of tuberculosis because increasing cerebrospinal fluid enhancement of the meninges being more effective when administered intramuscular as well as intrathecal administration.

Dosage.—Streptoduocin is administered only by intramuscular injection. Because of its dihydrostreptomycin content, the mixture must not be injected intravenously. The dosage is expressed in terms of total streptomycin base and should be exactly the same as that recommended for either of the components; for example, the usual dose in tuberculosis is 1 Gm. intramuscularly twice weekly in conjunction with the oral administration of 3 to 5 mg. of isoniazid per kilogram of body weight daily, or 12 Gm. of aminosalicylic acid daily.

ELI LILLY & COMPANY

Distreptocin: 5 and 20 cc vials, 1 and 5 Gm, respectively, of a powder composed of equal parts of streptomycin and dihydrostreptomycin as the sulfates.

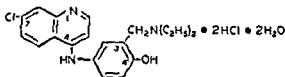
Pfizer Laboratories, Division of Chas. Pfizer & Company, Inc.

Combistrep: 5 and 20 cc vials 1 and 5 Gm, respectively, of a powder composed of equal parts of streptomycin and dihydrostreptomycin as the sulfates.

U. S. trademark 585,134.

ANTIMALARIAL AGENTS

AMODIAQUIN HYDROCHLORIDE.—Camoquin Hydrochloride (PARKE, DAVIS)—4-(7-chloro-2-methyl-2-methoxy-1-naphthyl)-2-methyl-4-hydroxyaniline
The structural formula is represented as follows



Physical Properties.—Amodiaquin hydrochloride is a yellow, odorless, bitter, crystalline solid, with a melting point between 150 and 160° (with decomposition). It is soluble in water, sparingly soluble in alcohol and very slightly soluble in benzene, chloroform and ether. The pH of a 1 per cent solution is between 4.0 and 4.8.

Actions and Uses.—Amodiaquin hydrochloride, a synthetic antimalarial agent, is equal to chloroquine phosphate in antimalarial potency and has the same relatively low toxicity. Like chloroquine, the activity of amodiaquin is limited to the erythrocytic stages of malaria (parasitemia). The drug is capable of producing a radical cure only for infection caused by *Plasmodium falciparum*; it abolishes the acute attack and eradicates the infection. In infections caused solely or complicated by *P. vivax* or *P. malariae*, it

in body tissues, where it is
in plasma; its concentration in erythrocytes is about twice that
in the plasma, the liver and
om which it is
ly excreted in

the urine after administration is discontinued. Clinical side effects are chiefly those of the gastro-intestinal tract (nausea, vomiting, salivation and diarrhea) and of the central nervous system (inco-ordination, spasticity and convulsions), but these seldom are encountered at therapeutic dosage levels. It does not produce discoloration of the skin. Complications have not been encountered in the presence of kidney or liver disease nor during pregnancy.

Dosage.—Amodiaquin hydrochloride is administered orally. Dosage is expressed in terms of the base. For the treatment of acute

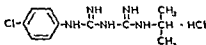
and above, adult dose. For suppression of endemic malaria, the usual dosage for adults is 0.4 to 0.6 Gm administered once every 2 weeks; for children, the dosage should be reduced according to age and spaced at the same interval.

PARKE, DAVIS & COMPANY

Tablets Camoquin Hydrochloride. 0.2 Gm. Each tablet contains the equivalent of 0.2 Gm. of amodiaquin base.

U. S. patents 2,474,818 and 2,474,821, U. S. trademark 500,228.

CHLOROGUANIDE HYDROCHLORIDE (LILLY) Hydrochloride (LILLY) - hydrochloride—The hydrochloride may be represented as follows:



Physical Properties.—Chloroguanide hydrochloride occurs as colorless crystals or as a white, crystalline powder. It is odorless, has a bitter taste and melts between 248 and 250°. One gram of this drug dissolves in about 75 cc. of water and in about 30 cc. of alcohol. It is insoluble in chloroform and ether.

Actions and Uses.—Chloroguanide hydrochloride is useful for the prophylaxis, suppression and treatment of malignant tertian (*Plasmodium falciparum*) malaria and for the suppression and treatment of the strains of benign tertian (*Plasmodium vivax*) malaria studied so far. The drug is only partially effective in preventing attacks of vivax malaria, erythrocytic forms appearing in the blood a short time after the drug is withdrawn. Other antimalarial drugs, such as chloroquine or quinacrine, are preferable in the treatment of

No toxic effects are observed in the usual dosage regimen, but

doses of 1 Gm. or more may produce vomiting, abdominal pain and diarrhea. Excessive doses may produce transient hematuria, epithelial cells and casts in the urine. Intramuscular injection of chloroguanide hydrochloride may result in local myonecrosis and inflammatory reactions. Large doses injected also may produce a temporary myelocytic reaction in the blood.

Different strains of plasmodia vary in their response to this as to other antimalarial agents. Therefore, the average dosage schedule indicated below is subject to modification according to the response of the individual strain.

Dosage.—A single dose of 0.3 Gm. weekly is effective in the suppression of falciparum and vivax malaria. For the prophylaxis of falciparum malaria, 0.1 Gm. may be given twice weekly; this dose is only partially effective against vivax malaria.

A dose of 0.1 Gm. three times daily, or 0.3 Gm. daily, for 10 days usually cures falciparum malaria. This dose usually is only partially effective against vivax malaria.

ELI LILLY & COMPANY

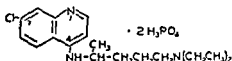
Tablets Guanafol Hydrochloride: 100 mg.

CHLOROQUINE

(THOMPSON-STEARN'S). —

amino)quinoline di

at 105° for 2 hours, contains not less than 98 per cent of $C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$. U.S.P. The structural formula of chloroquine phosphate may be represented as follows:



Physical Properties.—Chloroquine phosphate is a white, crystalline powder. It is odorless, has a bitter taste and slowly discolors on exposure to light. Its solution is acid to litmus paper, having a pH of about 4.5. It is freely soluble in water and almost insoluble

Considerable amounts are deposited in the organs, particularly those of the

slowly in the body, and more than a week after medication is discontinued

Chloroquine phosphate is active against the erythrocytic forms of *P. vivax* and *P. falciparum*. It does not prevent relapses in vivax

malaria, nor does it prevent the establishment of vivax infection when administered as a prophylactic. It is effective as a suppressive agent in vivax malaria and for the termination of acute attacks, lengthening the interval between treatment and relapse. In falciparum malaria, chloroquine phosphate abolishes the acute attack

especially, hepatic involvement often occur early in amebiasis, without clinical signs, some physicians consider it wise to administer a drug with systemic effect, such as chloroquine or emetine. While these drugs may give initial symptomatic relief, they should not be relied upon to effect a cure of the intestinal form of the disease, but should be supplemented by agents which reach the lower bowel in concentrations sufficient to establish a cure. These agents include certain arsenical and oxyquinoline drugs and some of the newer antibiotics. Chloroquine phosphate is preferable to injected emetine hydrochloride for the treatment of amebic hepatitis and abscess. It is not recommended for intestinal forms of amebiasis.

The drug is well tolerated in therapeutic doses and does not produce cinchonism or discoloration of the skin. However, mild headache, pruritus, visual disturbances and gastro-intestinal complaints may follow therapeutic doses. Blurring of vision and difficulty in focusing are observed occasionally following prolonged administration. None of the side reactions is serious, and all are reversible.

Dosage.—Chloroquine phosphate usually is administered orally either before or after meals.

A total of 2.5 Gm. in 3 days is sufficient to eradicate most infections with *P. falciparum*, and to terminate acute attacks of vivax malaria. An initial dose of 1 Gm. is supplemented by 0.5 Gm. after 6 or 8 hours and by 0.5 Gm. on each of the 2 succeeding days. Freedom from clinical attacks of vivax malaria is maintained by administration of suppressive doses of 0.5 Gm. at exactly 7-day intervals.

For the treatment of extra-intestinal amebiasis, 1 Gm. per day in divided doses is administered orally for 2 days, to saturate the tissues and to obtain a constant plasma concentration. Maintenance is then provided by 0.5 Gm. daily (0.25 Gm. twice daily) for 2 or 3 weeks.

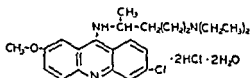
WINTHROP-STEARNs, INC.

Tablets Aralen Phosphate, 0.25 Gm.

U. S. patent 2,233,970

QUINACRINE HYDROCHLORIDE-U.S.P. — Atabrine Hydrochloride (WINTHROP-STEARNs) — 3-Chloro-7-methoxy-9-(1-methyl-4-diethylaminobutylamino)acridine dihydrochloride — Mepacrine Hydrochloride — "Quinacrine Hydrochloride contains not less than 98 per cent of $C_{23}H_{30}ClN_3O \cdot 2HCl \cdot 2H_2O$," U.S.P. The structural

formula of quinacrine hydrochloride may be represented as follows:



Physical Properties.—Quinacrine hydrochloride occurs as a bright yellow, crystalline powder. It is odorless and has a bitter taste. One gram dissolves in about 30 cc. of water. It is soluble in alcohol.

Actions and Uses.—Quinacrine hydrochloride destroys the asexual forms (trophozoites) of the causative organism in all types of malaria and, thus, checks the progress of the disease. Given during the first paroxysms of a benign tertian (*Plasmodium vivax*) attack it often will decrease the severity of the second paroxysm and completely prevent the appearance of the third. In ordinary cases of benign tertian malaria, and also in the more rare quartan (*P. malariae*) malaria, it produces better results than does quinine. Relapses are less frequent than with quinine and the period of treatment is shorter. Quinacrine hydrochloride is more effective than quinine in the treatment of malignant subtertian (*P. falciparum*) malaria. It is of value in the treatment of blackwater fever when quinine is contraindicated. Like quinine the drug partially destroys the sexual forms (gametocytes) of the malarial organisms and, thus, lessens the extent to which the patient may act as a reservoir from which mosquitoes may be infected. If taken faithfully in suppressive doses quinacrine hydrochloride lengthens the interval between relapses of malaria more effectively than quinine.

Quinacrine hydrochloride is effective in combating *Giardia lamblia* infestation, but the evidence that this organism is pathogenic for man or is the cause of diarrhea and other symptoms asso-

gastro-intestinal symptoms occur frequently. The drug does not cause visual or aural disturbances and, therefore, may be preferred to quinine. The circulatory system is not disturbed by therapeutic doses of quinacrine hydrochloride. The drug is not toxic to the liver or kidneys. Some patients claim that quinacrine hydrochloride is stimulating. A few psychotic attacks, some severe, have been attributed to the drug, but no permanent derangements have been recorded. The drug may be used safely in any stage of pregnancy though sometimes it is withheld in toxemia.

Quinacrine hydrochloride is absorbed readily from the intestine and is excreted slowly in the urine and feces. Usually, it is given by mouth but also may be given intravenously or, preferably, intramuscularly, if injection is necessary.

Dosage.—The following doses of quinacrine hydrochloride are administered in tablet form. Therapeutic dose in clinical malaria for adults and children over 8 years 0.2 Gm. and 1 Gm. of sodium

bicarbonate by mouth with 200 to 300 cc. of water (or an equal amount of sweetened tea or fruit juice) every 6 hours for five doses, then 0.1 Gm. three times daily for 6 days.

Children, 1 to 4 years. 0.1 Gm. three times daily for the first day, then 0.1 Gm. once daily for 6 days.

Children, 4 to 8 years. 0.2 Gm. three times daily for the first day, then 0.1 Gm. twice daily for 6 days.

Suppressive doses in malarious areas. Adults: 0.1 Gm. daily, preferably beginning 2 weeks in advance of exposure, and continuing for at least 4 weeks after last possible exposure in a malarious area.

Children: 50 mg. daily.

Suppressive doses in persons who have had attacks of vivax malaria within 6 months, and no quinacrine for 3 weeks.

Adults. 0.1 Gm. three times a day for 3 days, then 0.1 Gm. daily.

Children: 50 mg. three times a day for 3 days, then 50 mg. daily.

Note. Each dose, therapeutic or suppressive, should be taken with a full glass of water after a meal.

The technic of the intramuscular or intravenous administration must be studied before the method is used. Details are included in the circulars of manufacturers and in other publications.

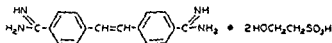
WENTHROP-STEARNES, INC.

Tablets Atabrine Hydrochloride. 0.1 Gm. plain and sugar coated.

U S patent 2,113,357. U S trademark 302,473

ANTIPROTOZOAN AGENTS

STILBAMIDINE ISETHIONATE.—1,1'-Stilbenedicarboxamide di-(β -hydroxyethanesulfonate).—The structural formula of stilbamidine isethionate may be represented as follows.



solves in alcohol to form 100 cc of solution is about 0.3 Gm.

tuberculosis, early African trypanosomiasis (except in cases with changes) and kala-azar, especially when tuberculosis, leishmaniasis, and lymphogranuloma venereum are the cause. The therapy is more effective in the treatment of Torula infections.

Stilbamidine isethionate is detectable in the blood and urine in relatively high concentrations within a few minutes after either oral administration or parenteral injection of a single maximum tolerated dose. The blood level falls rapidly within 30 minutes, despite differences in the maximum dose tolerated by various routes. A rapid fall in urinary excretion occurs after the first 2 hours. With daily administration, the amount eliminated tends to remain unchanged regardless of the dosage. Its rapid disappearance from the blood is attributed only partially to urinary excretion. The unusual adsorptive effects of the drug on proteins of the serum, plasma and other body fluids is believed to account for its rapid disappearance from the blood. Current methods for its detection are not sufficiently accurate to permit definite conclusions concerning its metabolic fate in the body. The amounts fixed in the tissue proteins or viscera have not been determined. Penetration of the meningeal barrier by the drug is poor. Intrathecal administration is not feasible because of its local irritant effect, and intramuscular injection produces local inflammation and pain at the site of administration. Concentrated solutions administered intravenously may produce thrombophlebitis.

During or immediately following intravenous injection, many or all of the following symptoms and reactions have been elicited or observed, approximately in the order of decreasing incidence: fall in blood pressure; rapid, thin pulse; facial flushing, dizziness; salivation; sweating, headache; nausea, vomiting, dyspnea; formication, syncope, lethargy; fecal and urinary incontinence, and edema of the eyelids and face. These side reactions usually are transitory and disappear within 10 to 30 minutes. They are less severe with intramuscular injection and slow intravenous drip. In kala-azar, a modified Herxheimer reaction may occur within 6 hours following the first injection. The occurrence of a unique neuropathic syndrome involving progressive sensory changes in the distribution of the trigeminal nerve is a late toxic manifestation attributed to stilbamidine. Two to five months after a course of therapy, patients may gradually observe paresthesia, anesthesia, hypalgesia and numbness (usually confined to the face). Sensibility to light touch is decreased, but usually pain, temperature and pressure sense remain intact. The same findings may apply to the neck and waist. The incidence of occurrence of these late neuropathic effects is considered to be above 50 per cent. The symptoms often disappear slowly, but they may persist indefinitely. The neurotoxic effects of the drug have been sufficiently troublesome to influence physicians against using it for treatment of trypanosomiasis and leishmaniasis. Freshly prepared solutions of the drug administered in therapeutic doses have not been associated with hepatic or renal injuries, which formerly occurred following the use of ready-made

solutions exposed to ultraviolet light. However, both hepatic and renal function should be determined prior to therapy, as stilbamidine is contraindicated in hepatic or renal dysfunction. Partial deterioration of the drug is produced by the action of ultraviolet light on the unsaturated stilbene linkage. Solutions exposed to heat or light contain toxic deterioration products, but such deterioration does not occur when the drug is stored in dry form away from heat and light. Freshly prepared solutions should be protected similarly. Following injection, patients should be warned against excessive exposure to sunlight on the premise that stilbamidine remaining in the skin may be altered and the toxic products thus formed may initiate selective nerve injury.

Dosage.—Stilbamidine isethionate is administered intravenously by continuous, slow drip. A freshly prepared solution of the dose to be used, dissolved in about 200 cc. of either 5 per cent dextrose in water for injection or isotonic sodium chloride solution, is infused over a period of 2 hours. Slow infusion is essential to avoid a fall in blood pressure. The solution should be protected from light by covering the container with black paper or a heavy towel.

The suggested average adult dose is 150 mg., repeated every 24 to 48 hours for a course of about 15 injections. It is advisable to initiate therapy with a 50 mg. dose, increasing this to 100 mg. for the second dose and to 150 mg. for the third dose. It is suggested that the patient be placed on a low protein, low purine-type diet, which is thought to avoid certain antidimidine effects of proteins high in arginine. The dosage and frequency of administration of the drug should be altered when necessary to meet the requirements of the individual patient. The physician should become familiar with the reactions and side effects expected from the use of stilbamidine.

THE WM. S. MERRELL COMPANY

Powder Stilbamidine Isethionate: 150 mg. ampuls

Antimony Compounds

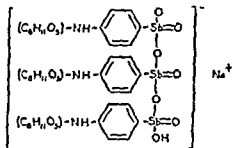
The pharmacologic effects of antimony preparations depend to some extent on the rapidity with which antimony is freed from the complex compound. All organic antimony compounds, particularly if injected rapidly into the blood stream, may produce a transient fall in systemic blood pressure, partly because output of the left ventricle is diminished and partly because the splanchnic vessels are dilated. At the same time, there is a rise in pulmonary blood pressure. Large doses depress respiration.

The mechanism by which antimony compounds cure leishmaniasis is unknown; it does not seem to be the result of a direct action on the parasites.

The pentavalent organic antimony compounds are less toxic than trivalent organic antimony compounds and may be injected intramuscularly. They are more effective in the treatment of most forms of leishmaniasis (kala-azar) but are of little value in South

American leishmaniasis (mucocutaneous) and against the helminths of schistosomiasis (bilharziasis) and filariasis. Trivalent antimony also has been preferred for the treatment of granuloma inguinale, but antimony therapy in this disease has been superseded by the use of antibiotics. For the treatment of trypanosomiasis antimony compounds have been replaced largely by pentavalent organic arsenicals.

STIBAMINE GLUCOSIDE.—Neostam Stibamine Glucoside (BROUHAUS WELLCOME).—A nitrogen glucoside of sodium *p*-aminobenzenesbionate.—A product of incompletely defined structure prepared by the condensation of *p*-aminobenzoic acid and glucose is absolute ally as a trimer linked through the stibonic group, $C_{36}H_{49}O_{22}Na_3Sb_3$. The structural formula of stibamine glucoside may be represented as follows:



Physical Properties.—Stibamine glucoside is an odorless, pale cream to light buff, amorphous powder. It is soluble in water. The pH of a 6 per cent solution is between 8.5 and 9.0.

Actions and Uses.—Stibamine glucoside shares the antiprotozoan action of other pentavalent organic antimony compounds.

Stibamine glucoside, in common with other pentavalent organic antimony compounds, produces fewer side reactions than trivalent organic antimony and may include vomiting (about 10 per cent), diarrhoea. Anaphylactic eruption, husky voice may be encountered after the rare but serious reaction medication.

Stibamine glucoside is contraindicated in the presence of pneumonia, nephritis, jaundice or ascites.

Dosage.—Stibamine glucoside is administered intravenously, but may be given intramuscularly when superficial veins are not accessible. The average dose is calculated on the basis of 0.1 Gm. per 45.4 Kg (100 lb) of body weight, administered as a freshly prepared 4 per cent solution (0.1 Gm. in 2.5 cc. of sterile distilled

water). It is rarely necessary to exceed a maximum single dose of

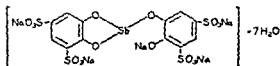
is considered likely because they have had previous treatment, it is advisable to employ an initial dose of 0.05 Gm per 45.4 Kg of body weight, and to increase subsequent doses gradually as tolerance is established.

Solutions must be prepared from freshly opened containers. The solution should not be warmed for injection, nor used more than 1 hour after its preparation.

BURROUGHS WELLCOME & COMPANY, INC.

Neostam Stibamine Glucoside. 0.1 Gm vials. Each vial contains the stated quantity of stibamine glucoside hermetically sealed under nitrogen to preserve stability.

U. S. trademark 503,747.



Physical Properties.—Stibophen occurs as a white, crystalline, odorless powder. It is affected by light. It is freely soluble in water,

guanine than in the later stages when there is scar formation. It is necessary to continue the treatment for some time after all traces

cc., second day 3.5 cc. and on the third, fifth, seventh, ninth, eleventh, thirteenth and fifteenth days 5 cc., a total of 40 cc. of 6.3 per cent solution. In a week or two following healing, the course may be repeated and thereafter the drug is given once a week and then every 14 days for several weeks to prevent relapse.

WINTHROP-STEARNs, INC.

Solution Fuadin: 5 cc ampuls. A solution containing 63 mg. of stibophen and not more than 0.12 per cent of sodium bisulfite in each cubic centimeter.

U. S. trademark 304,950.

Arsenic Compounds

Some of the compounds listed in this chapter contain pentavalent arsenic; in others, the arsenic is trivalent. A typical arsenic reaction is produced only by trivalent arsenic. Compounds containing pentavalent arsenic cause this reaction after they have been reduced to trivalent arsenic by the body. The rate at which this reduction occurs varies greatly with different compounds. The desirable as well as the undesirable effects produced by some of these compounds are due to the arsenic which is slowly rendered active; in others the therapeutic effects are due, at least in part, to the unaltered molecules. Arsenic therapy has proved particularly useful in diseases caused by protozoa. Inorganic arsenic kills protozoa, but the doses required are too large to be administered safely. The organic compounds are less toxic to mammals and more toxic to protozoan parasites than the inorganic preparations.

Organic arsenic compounds possess certain advantages over inorganic ones. Compounds that are effective by the liberation of arsenic free it slowly. Some organic compounds have prolonged contact with the foreign parasites because they remain in the circulating blood longer than do inorganic compounds. Other compounds of this group are specifically etiotropic; that is, they have a much greater affinity for the parasites causing the disease than they have for the tissues of the host.

Arsenic preparations used intravenously are subject to the federal law covering serums, viruses, toxins and analogous products.

Compounds Containing Pentavalent Arsenic

The pentavalent arsenic compounds have been used as amebicides and, more rarely, for the treatment of syphilis of the central nervous system. In the treatment of trichomonas vaginitis, the arsenicals seldom are used because there is a high risk of toxic effects without compensatory therapeutic effect. The compounds containing pentavalent arsenic are comparatively nontoxic when introduced into the animal system until changes liberate the arsenic. When they are decomposed slowly, they produce favorable effects. If the reduction takes place with greater rapidity, they may produce ordinary arsenic poisoning.

Common side reactions to the pentavalent arsenicals are gastrointestinal symptoms, hepatitis and such cutaneous disturbances as are caused by the arsphenamines, for example, urticaria, erythemas and hemorrhagic eruptions.

Such changes may be observed prior to and during the treatment.

Ordinarily, the reaction is slow, and such changes may be observed during the treatment.

GLYCObIARSOL-N.F.—Milibic (WINTHROP-STEARNs)—Bismuth β -Glycolylarsanilate—"Glycobiarsol yields, calculated to the anhydrous basis, not less than 97 per cent and not more than 103 per cent of $C_8H_9AsBiNO_6$ " N.F. The structural formula of glycobiarsol may be represented as follows.



Physical Properties.—Glycobiarsol is an odorless, yellowish white to flesh-colored, amorphous powder that decomposes when heated. It is very slightly soluble in alcohol and water and insoluble in benzene, chloroform and ether. The pH of a saturated solution is between 2.8 and 3.5.

Actions and Uses.—Glycobiarsol is an amebicide recommended only for the treatment of intestinal amebiasis. Low solubility and poor absorption are responsible for its low toxicity. These properties limit its usefulness to the prevalent intestinal form of the disease. Therefore, it should be supplemented by other therapy in the presence of amebic hepatitis and/or deep-seated, cicatrized ulceration of the intestine.

The compound produces a characteristic reaction when tested by reduced peristalsis. It must be administered on an empty stomach to prevent absorption from the intestine.

Dosage.—The drug is administered in capsules, three times a day, after meals, for 7 days. The capsules constitute the dose. The treatment should be continued until findings persist. Larger doses may be employed during frank diarrhea to obviate rapid elimination of the drug.

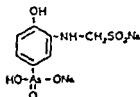
WINTHROP-SEARNS, INC.

Tablets Milibis: 0.5 Gm.

U. S. patent 1,934,017.

PHENARSONE SULFOXYLATE.—Aldarsone (ABBOTT).—Sodium sulfoxylate.—Phen-3-amino-4-hydroxy- mixed with sodium bicarbonate 7.0 to 18.5 per cent one sulfoxylate may

of aldarsone. . . .
be represented as follows.



Physical is a white, odorless, amorphous alkalis and alkali salt soluble in alcohol and ether. The pH of a 1% between 7.0 and 7.4.

Actions and Uses.—Phenarsone sulfoxylate, a pentavalent arsenical may be used in the treatment of *Trichomonas vaginalis* vaginitis nervous system.

However, against nervous system, 1 of sterile distilled week The in-

jections may be given continuously, 1 to 50 weeks. Concurrent bismuth therapy may be employed during part of the phenarsone sulfoxylate treatment

For the treatment of trichomonas vaginitis, phenarsone sulfoxylate may be administered by insufflation of the powder (with kaolin) and in the form of suppositories.

ABBOTT LABORATORIES

Aldarsone with Kaolin: 0.5 Gm phenarsone sulfoxylate and 2.5 Gm. kaolin packaged in glass tubes suitable for use with insufflator.

U. S. patent 2,074,757. U. S. trademark 338,986.

Compounds Containing Trivalent Arsenic

According to Ehrlich's view, only trivalent arsenic is significantly toxic to spirochetes, trypanosomes, etc. Of compounds containing trivalent arsenic, only those are listed whose toxicity is reduced by

their introduction into certain molecules. These compounds have a special affinity for certain lower organisms, while their toxicity in higher animals is comparatively low.

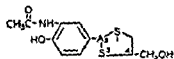
Administration of the drug when the patient has a full stomach or has not been prepared by catharsis may result in untoward response. Because idiosyncrasies of patients also cause reactions, it is well to start the use of arsenicals with small doses. Improper preparation or administration of the drug may add to the toxicity. If the manufacturer's directions are followed and reactions continue to occur, the cause should be sought elsewhere.

Occurrence of the Herxheimer reaction after the first injection of the arsphenamines in active cases of syphilis is not a contraindication. This phenomenon comprises rise in temperature, headache, possible nausea, malaise and accentuation of the cutaneous and mucous membrane symptoms. Contraindications to further use are itching of the skin, urticaria, conjunctivitis, jaundice, fixed areas of dermatitis that flare up with each injection, generalized exfoliative dermatitis, purpura hemorrhagica, aplastic anemias, acute yellow atrophy and encephalitis.

The patients should be questioned prior to each administration concerning the appearance of pruritis or cutaneous eruptions following the previous injection. Urine examination always should precede readministration. Dimercaprol (BAL) has been used in the treatment of hemorrhagic encephalitis and dermatitis due to arsenotherapy. Further discussion of this technic may be found in the chapter on unclassified therapeutic agents.

Arsphenamines are contraindicated or should be used with special caution in nonsyphilitic diseases of the eye, in severe affections of the heart and blood vessels, the lungs and the kidneys and in advanced degenerative processes in the nervous system. They also should be used with caution in infants. Arsphenamine should not be used in acute luetic optic neuritis or interstitial keratitis until after preliminary antiluetic therapy with either penicillin or bismuth.

ARSTHINOL.—Balarsen (ENDO) — Cyclic 3-hydroxypropylene ester of 3-acetamido-4-hydroxydithiobenzenearsonous acid ~2-(3'-Acetamido-4'-hydroxyphenyl)-1,3-dithia-2-arsacyclopentane-4-methanol.—The structural formula of arsthinol may be represented as follows:



Physical Properties.—Arsthinol is a white, odorless, microcrystalline powder, with a melting point between 164 and 166°. It is very slightly soluble in ether and water. The amount that dissolves in alcohol to form 100 cc of solution is 2.7 Gm.

Actions and Uses.—Arsthinol is a trivalent arsenical with indica-

tions somewhat similar to the pentavalent arsenicals that were available previously for oral use. Pentavalent arsenicals presumably are reduced to trivalent compounds in the body and act in the latter form.

Arsthinol, when administered by the oral route, has been demonstrated to be effective against intestinal amebiasis and yaws. There is no adequate evidence to indicate that the substance is effective against nonintestinal amebiasis, but it may be of value against other intestinal protozoa. However, the latter claims require further substantiation.

Dosage.—Arsthinol should be given in courses lasting 5 days. The daily oral dose is 10 mg. per kilogram of body weight, with a maximum of 500 mg. in 24 hours. Ordinarily the entire daily dose is taken following breakfast.

ENDO PRODUCTS, INC.

Tablets Balarzen: 100 mg.

OXOPHENARSINE HYDROCHLORIDE-U.S.P. — *Mapharsen* (PARKE, DAVIS). — 3-Amino-4-hydroxyphenylarsineoxide hydrochloride. — "Oxophenarsine Hydrochloride, dried in a vacuum desiccator over phosphorus pentoxide for 24 hours, contains not less than 30 per cent and not more than 32 per cent of total arsenic (As).

"Oxophenarsine Hydrochloride usually is distributed as a mixture with buffering agents and suitable substances to render its solution physiologically compatible with human blood. Each such mixture contains total arsenic equivalent to not less than 92.5 per cent and not more than 107.5 per cent of the labeled amount of Oxophenarsine Hydrochloride." U.S.P. The structural formula of oxophenarsine hydrochloride may be represented as follows:



Physical Properties.—Oxophenarsine hydrochloride is a white, odorless powder, soluble in water and in dilute alkalis and in dilute mineral acids.

Action. — Oxophenarsine hydrochloride is proposed for the treatment of constant parasyphilitic lesions and reversal of positive Wassermann reactions in a high percentage of cases. It is believed that an oxophenarsine compound is the immediate spirocheticidal agent formed from the arsphenamines in the host organism after injection. Thus it becomes understandable that the therapeutic action of oxophenarsine hydrochloride is about ten times greater than that of the arsphenamines. For this reason, the dosage of oxophenarsine hydrochloride, and, therefore, its

toxic effects, are considerably less than those of the arsphenamines.

The initial treatment dose is 0.03 Gm. for adults.

is 0.06 Gm. Injections may be given every 4 or 5 days, since the drug is excreted very rapidly from the kidneys. For children, the initial dose should not exceed 0.5 mg. per kilogram of body weight; the total dose should average between 0.5 and 1 mg. per kilogram of body weight.

PARKE, DAVIS & COMPANY

Mapharsen: 40 and 60 mg. ampuls and 0.6 Gm. multiple dose ampuls. *Caution: These ampuls are hospital packages and represent either 10 doses at 60 mg. or 15 doses at 40 mg.* Each of the ampuls of mapharsen contains the stated amount of the arsenical, oxophenarsine hydrochloride admixed with anhydrous sodium carbonate, anhydrous sucrose and ascorbic acid.

U. S. patents 2,092,028, 2,092,036, 2,221,817 and 2,280,132. U. S. trademark 299,173.

Bismuth Compounds

Until 1921, bismuth was used mainly in the treatment of intestinal infections.

treatment of syphilis. Its efficacy is between that of mercury and that of arsphenamine. Since the advent of more effective remedies, such as penicillin, bismuth seldom is employed in the treatment of syphilis; its use may be indicated in patients who are sensitive to other forms of treatment.

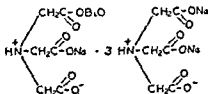
The best results with bismuth therapy of syphilis have been achieved with intramuscular injection. Intravenous injections are contraindicated because the therapeutic dose approaches too closely to the toxic dose. The compounds of bismuth that have the best spirocheticidal value are those that keep the level of bismuth in the blood stream continuously at the high level indicated by 0.002 Gm. or more of metallic bismuth excreted in the urine each day. The compounds tested are as follows:

absorption than insoluble suspensions of bismuth salts, but they are not absorbed and excreted as rapidly as the soluble preparations. Thus, they combine some of the advantages of both the soluble and insoluble preparations. If water solutions are injected two or three times a week, the bismuth is absorbed rapidly and high concentration maintained in the blood stream. Oil suspensions effect slower but more prolonged concentration in the blood, thus requiring injections only once a week. Some oil solutions, although similar, are absorbed more rapidly. Bismuth salicylate is absorbed slowly, and its bismuth effect thereby is delayed. Small amounts continue to be excreted for months after injections are stopped. It is doubtful, however, that this long excretion indicates a therapeutic level of the drug in the body.

In intramuscular injections of the bismuth salts the needle should be inserted in the upper and outer quadrant near the inner angle of

sician should then aspirate back with the plunger of the syringe several times in order to be sure that the needle is not in a vein or in an artery. This having been ascertained, the needle butt is held firmly in place with the thumb and first finger of the left hand while the injection is made with the right hand. This will go far toward obviating many of the distressing venous emboli and arterial emboli that have been reported.

BISMUTH SODIUM TRIGLYCOLLAMATE.—Bistrimate (CARROLL DUNHAM SMITH).—Sodium bismuth complex of nitrilotriacetic acid.—A double salt of sodium bismuthyl triglycollamate and disodium triglycollamate containing approximately 18.3 per cent of bismuth. The structural formula of bismuth sodium triglycollamate may be represented as follows:



Physical Properties.—Bismuth sodium triglycollamate is a white, odorless, crystalline powder with a somewhat salty taste. It is soluble in water but insoluble in alcohol and ether.

employed for the same purpose. Bismuth sodium triglycollamate also has proved useful in some cases of lupus erythematosus, lichen planus and scleroderma. The urine should be examined frequently during the use of this drug.

Bismuth sodium triglycollamate is subject to the contraindications of bismuth preparations in general and should be discontinued in the presence of nephritis upon the appearance of albuminuria or gastro-intestinal upset.

be reduced temporarily to the lower figure to overcome gastro-intestinal disturbances that are encountered occasionally.

CARROLL DUNHAM SMITH PHARMACAL COMPANY

Tablets Bistrimate: 0.41 Gm. Each tablet contains the equivalent of 75 mg. of bismuth.

U. S. patent 2,348,984.

Iodine Compounds

DIODOHYDROXYQUIN—U.S.P.—Diodoquin (SEARLE)—Yodoxin

The structural formula of diodohydroxyquin may be represented as follows.



Physical Properties.—Diodohydroxyquin is a colorless or light yellowish to tan, microcrystalline powder. It is odorless or has a faint odor and is stable in air. It melts with decomposition, is almost insoluble in water and is sparingly soluble in alcohol and ether.

Actions and Uses.—Diodohydroxyquin is used as an antiprotozoan agent in intestinal amebiasis and in the treatment of *Trichomonas hominis* (intestinalis) infections.

Dosage.—Adults: For amebiasis, 2 Gm. daily in divided doses for a period of 20 days usually is recommended; 0.4 to 0.6 Gm. daily may be adequate in asymptomatic carriers.

B. L. LEMKE & COMPANY, INC.

Powder Yodoxin: 25, 100 and 454 Gm bottles for compounding use; and in bulk.

Tablets Yodoxin: 0.21 Gm.

G. D. SEARLE & Co.

Tablets Diodoquin: 0.65 Gm.

U. S. trademark 336,484.

6

Autonomic Drugs

The designation "autonomic drugs" is applied to drugs that either mimic or oppose the peripheral effects of nerve impulses of the autonomic (visceral efferent, vegetative, involuntary) nervous system. These drugs have been grouped into four main classes on the bases of (a) the two anatomic divisions of the autonomic system, namely, the sympathetic (thoracolumbar) and the parasympathetic (craniosacral), and (b) the two principal effects, stimulation and depression, upon the given division. Accordingly, the four principal classes are (1) sympathomimetic (adrenergic), (2) sympatholytic (adrenergic blocking), (3) parasympathomimetic (cholinergic) and (4) parasympatholytic (cholinergic blocking). Since the two divisions are, on the whole, mutually antagonistic, it is seen that drugs of classes (1) and (4) have certain effects in common, thus atropine, which is parasympatholytic, and epinephrine, which is sympathomimetic, both dilate the pupil. Similarly (2) and (3) sometimes have identical effects.

The quaternary ammonium compounds produce mixed autonomic effects by partial block of nervous impulses through certain sympathetic and parasympathetic ganglia. They reduce vasospasm and arterial blood pressure but also produce loss of accommodation and decrease in gastro-intestinal motility and alter urinary bladder function.

The effects of the drugs of the same group differ quantitatively

to sweat glands and certain vascular beds, the splanchnic fibers to the adrenal medulla and also the cerebrospinal motor fibers to skeletal muscle.

Fibers of the sympathetic branch ramify widely through several ganglionic cells so that a diffuse discharge is possible, whereas parasympathetic fibers have terminal ganglia near to the innervated organ, so that impulses are more discrete in their effect. Furthermore, cholinesterase causes rapid destruction of acetyl-

the adrenal medulla does for epinephrine and levasterenol (nor-epinephrine).

SYMPATHOMIMETIC (ADRENERGIC) AGENTS

These drugs that impulses convey sympathetic nervous system. Most of these agents are aromatic compounds, and their similarity of action is explained by a similarity of chemical structure in that the benzene nucleus which constitutes the aromatic portion of the molecule is separated from an amino nitrogen atom by two carbon atoms of the aliphatic portion of the molecule. Certain capabilities for substitution in either the aromatic or aliphatic portions have led to the synthesis of a large number of sympathomimetic amines, which, while retaining sympathomimetic activity, exhibit new properties that are chemically useful. Chemically dissimilar compounds that possess sympathomimetic activity also have been developed.

Sympathomimetic agents can be grouped according to their aliphatic portions. Thus, epinephrine and norepinephrine have identical aromatic portions, ephedrine and phenylpropanolamine and tyramine and hydroxyamphetamine are similarly paired. Again, epinephrine and phenylephrine have identical aliphatic portions; amphetamine and hydroxyamphetamine are similarly paired. Amphetamine, hydroxyamphetamine and tuaminoheptane possess, as a common feature, an aliphatic 3-carbon chain with an amino group attached to the middle carbon atom; their differences lie in

agents exist the dextrorotatory form may differ greatly in activity from the levorotatory form.

Ephedrine, amphetamine and phenylephrine differ from epinephrine in that their excitatory actions are diminished only, and not

tween other members of this class of autonomic drugs. Ephedrine, in contrast to epinephrine, is effective orally, has more prolonged action, produces less arteriolar constrictor effect, fails to act if given too frequently (tachyphylaxis) and affects skeletal muscle. The central stimulatory effects of ephedrine and amphetamine are

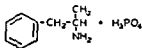
bronchioles, stomach, intestine, bladder and ureter; contraction of smooth muscle sphincters, the splenic capsule and pregnant uterus; constriction of blood vessels other than coronary; inhibition of the secretion of certain glands; and increased cardiac rate and output. Their principal therapeutic use is based on their most prominent actions; namely, those on the heart, blood vessels and certain smooth muscles.

The cardiovascular response to a sympathomimetic amine frequently is modified by the presence of a previous dose of the same or another amine. The pressor response may be increased, decreased or inverted to a depressor action. For instance, phenylpropylmethylamine pressor action is inverted to depressor action by the presence of hydroxyamphetamine, but not by other amines. Epinephrine, although the most potent pressor amine, dilates capillaries, perhaps accounting for the hypotension seen to follow its transient vasoconstriction of the arterioles. Reversal of its constrictor action occurs when its use is preceded by administration of adrenergic blocking agents.

Ventricular arrhythmias, even fibrillation, may follow the use of epinephrine, particularly during surgical anesthesia, and its use may be dangerous in such circumstances. In patients with medical or surgical shock, it may aggravate the underlying cause. It should not be given in the presence of emphysematous bronchial asthma. Pressor effects of any of these compounds are to be avoided in hyperthyroidism and hypertensive heart disease.

Milder side reactions of anxiety, tension, restlessness, insomnia, tremor, weakness and palpitation also may interfere with the clinical use of these compounds. In this group the claimed advantage of one compound over another depends largely on the purpose for which it is employed, an undesirable side effect in one instance becomes a useful therapeutic action in another.

AMPHETAMINE PHOSPHATE. N.F.—Raphetamine Phosphate (STRASENBURGH).—*dl*-Monobasic Amphetamine Phosphate—Racemic Amphetamine Phosphate—"Amphetamine Phosphate, dried at 105° for 2 hours, contains not less than 98 per cent of $C_9H_{13}N H_3PO_4$." *N.F.* The structural formula of amphetamine phosphate may be represented as follows



Physical Properties—Amphetamine phosphate is a white, odorless powder with a bitter taste. It sinters at about 150°, becomes an amorphous mass as heating is continued and decomposes at about 300°. It is freely soluble in water, slightly soluble in alcohol and

practically insoluble in benzene, chloroform and ether. The pH of a 10 per cent solution is about 4.6.

Actions and Uses.—Amphetamine phosphate shares the actions and uses of amphetamine sulfate. Its one advantage, greater solubility, is significant only in the preparation of solutions for injection. For the indications for its use see the monograph on amphetamine sulfate.

Dosage.—Doses of amphetamine phosphate approximately 20 per cent greater by weight than those recommended for amphetamine sulfate provide the same amount of the base. Because the average oral dose seldom exceeds 10 mg., the difference between the prescribed amount of the phosphate and sulfate is likely to be undetectable clinically. Theoretically, 12 mg. of amphetamine phosphate represents the approximate equivalent of 10 mg. of amphetamine sulfate. As an analeptic, the drug is administered intravenously or intramuscularly in doses of 20 to 50 mg. every 30 to 60 minutes until consciousness is restored. The same precautions and contraindications must be observed as in the case of other sympathomimetic amine compounds.

KEITH-VICTOR PHARMACAL COMPANY

Tablets Amphetamine Phosphate: 5 mg.

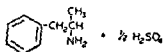
R. J. STRASBURGH COMPANY

Elixir Rapphetamine Phosphate: 473 cc. and 3.78 liter bottles. A flavored alcohol solution containing 1.25 mg. of amphetamine phosphate in each cubic centimeter

Solution Rapphetamine Phosphate 1%: 10 cc. vials. A solution containing 10 mg. of amphetamine phosphate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Tablets Rapphetamine Phosphate: 5 mg.

100.5 per cent of $(C_9H_{13}N)_2H_2SO_4$. U.S.P. The structural formula of amphetamine sulfate may be represented as follows:



Physical Properties.—Amphetamine sulfate occurs as a white, odorless powder that is freely soluble in water and slightly soluble in alcohol. Its aqueous solution is neutral to litmus.

Actions and Uses.—Amphetamine sulfate has been employed widely in the treatment of narcolepsy, in controlling the oculogyric crises and various other manifestations of postencephalitic parkinsonism and as an adjunct in the treatment of alcoholism, but its most extensive therapeutic application has been in the

treatment of certain depressive conditions, especially those characterized by apathy and psychomotor retardation

The drug's stimulating effect on the central nervous system renders it effective in the symptomatic treatment of many mild psychogenic depressive states, particularly those attending childbirth,

disorders the use of the drug should be subordinated to treatment of the underlying causes

Amphetamine sulfate also may be of value to a lesser extent in symptomatic treatment of more severe depressions accompanying certain major psychopathic conditions. While the drug is useful in the treatment of depressive states, it does not alter the course of the underlying psychosis in major psychopathic conditions. Obviously, severely depressed psychopathic patients should be institutionalized.

Again due to its ameliorative influence on mental depression, amphetamine is useful as an adjunct in the treatment of alcoholism. In chronic alcoholism, especially, it may provide a desirable means of interrupting the vicious alcoholic cycle, thus permitting the institution of more fundamental psychotherapeutic measures. In acute alcoholism, with or without accompanying psychosis, the drug may be useful occasionally in combating pathologic intoxication. (In alcoholic psychoses best results are reported where the psychosis is of recent origin.)

In addition, the drug is effective in the symptomatic treatment of orthostatic hypotension. It is not recommended for use in spastic colitis or pyloric spasm.

In suitable cases, amphetamine sulfate is useful as an appetite-depressant for obtaining weight reduction in the management of obesity. It has been found to allay the sensation of hunger, although there is still some doubt as to the mechanism of this action. It may assist some individuals in adhering to a strict dietary regimen and is especially valuable in those patients in whom over-

occurred in some such cases. Except when administered under the strict supervision of the physician, its use is not recommended for developing a sense of exhilaration, increased energy and capacity for work, nor as a "pick-me-up" following temporary alcoholic overindulgence.

Because of the pharmacologic nature of amphetamine, its administration may produce overstimulation, restlessness, sleeplessness and gastro-intestinal disturbance, overdosage may be followed by chills, collapse and syncope. Amphetamine should be administered with caution in the presence of hypertension or cardiovascular

tion are rare.

Dosage.—Since effective doses vary considerably, the dose should be small (5 mg. or less) and should be given frequently until a definite effect appears. The drug is particularly important in the treatment of depressive states. In most cases, it is desirable to administer the drug in divided doses. To avoid interference with sleep, the final daily dose ordinarily should be given not later than 4 p.m. The usual therapeutic dose is from 5 to 30 mg., though larger doses occasionally are given.

To depress the appetite in overweight, doses of 5 to 10 mg. three times daily, preferably administered $\frac{1}{2}$ to 1 hour before each meal, usually are sufficient. The dosage should be adjusted to individual needs and should be the minimum necessary to produce the desired reduction of appetite. In no instance should it exceed 30 mg. daily. To minimize the possibility of initial overstimulation the physician should begin treatment with smaller doses, increasing them gradually until optimal results are achieved.

A capsule containing 15 mg. of amphetamine sulfate incorporated into variably coated pellets which permit continuous release of the drug over a period of 8 to 10 hours, thus prolonging the therapeutic effect for 10 to 12 hours, may be administered once daily in the morning to adults in place of ordinary medication in divided amounts. In patients with hypermotility of the intestinal tract, the duration of the effect occasionally may be shortened so that the usual tablet form may be more effective in such cases.

BIORGANIC LABORATORIES, INC.

Powder Amphetamine Sulfate: 100 Gm., 1 Kg. and bulk packages for compounding use.

THE EVRON COMPANY, INC.

Tablets Amphetamine Sulfate: 5 and 10 mg.

GOLD LEAF PHARMACAL COMPANY, INC.

Tablets Amphetamine Sulfate: 5 and 10 mg.

KEITH-VICTOR PHARMACAL COMPANY

Tablets Amphetamine Sulfate: 5 and 10 mg.

LINCOLN LABORATORIES, INC.

Tablets Amphetamine Sulfate: 10 mg.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Amphetamine Sulfate: 5 and 10 mg.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Amphetamine Sulfate: 10 mg.

SMITH, KLINE & FRENCH LABORATORIES

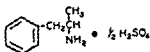
Spansule Sustained Release Capsules Benzadrine Sulfate. 15 mg

Powder Benzadrine Sulfate: 2.5 Gm. bottles.

Tablets Benzadrine Sulfate: 5 mg and 10 mg.

U. S. trademarks 337,407, 562,210 and 390,757 (Spansule)

DEXTRO AMPHETAMINE SULFATE-U.S.P.—*Dexadrine Sulfate* (SMITH, KLINE & FRENCH)—*d*-1-Phenyl-2-aminopropane Sulfate—"Dextro Amphetamine Sulfate, the dextrorotatory isomer of amphetamine sulfate, dried at 105° for 2 hours, contains not less than 98 per cent and not more than 100.5 per cent of $(C_9H_{13}N)_2 \cdot H_2SO_4$ " U.S.P. The structural formula of dextro amphetamine sulfate may be represented as follows



Physical Properties—Dextro amphetamine sulfate is a white, odorless, crystalline powder. Its 1 in 20 solution is acid to litmus and has a pH between 5.0 and 6.3.

Actions and Uses—Dextro amphetamine sulfate has the same actions and uses as the racemic compound, amphetamine sulfate, but exerts a predominantly greater stimulating effect on the central nervous system. Because of its relatively weak peripheral activity, it is regarded generally as less toxic than previously introduced sympathomimetic amines that are commonly employed clinically. Thus, it seldom gives rise to undesirable side effects such as changes in blood pressure, tremor, tachycardia and mydriasis. Dextro amphetamine sulfate, therefore, is useful by oral administration for the treatment of narcolepsy, postencephalitic parkinsonism and as an adjunct in the management of acute and chronic alcoholism and alcoholic psychoses of recent origin, it is employed also for the symptomatic treatment of depressive states (especially to elevate the mood in early, mild, psychogenic depression characterized by apathy and psychomotor retardation and, to a variable or lesser extent, in psychoneuroses and in severe depressions involving certain major psychopathic conditions of institutionalized patients). The drug also may be used as a stimulant in the management of certain behavior problems of children, but it is not useful in schizophrenics and has an unfavorable effect on children with psychopathic personalities. The appetite-depressant effect of the drug also is useful as an adjunct in the dietary management of obesity.

Dextro amphetamine sulfate should not be employed as a stimulant by normal persons to mask fatigue caused by physical exertion or overwork. It should be used with caution in patients hypersensitive to sympathomimetic amines, those with coronary or cardiovascular disease and those with severe hypertension. It is contraindicated in the presence of hyperexcitability and agitated

prepsychotic states. If administered too late in the day, the drug may interfere with sleep.

Dosage.—Dextro amphetamine sulfate is administered orally. In the treatment of depressive states or alcoholism, the usual daily dosage ranges from 5 to 15 mg., administered as ordinary tablet or liquid medication in two or three doses at intervals of either 4 or 6 hours. The initial dose should be given on awakening so as to complete the total daily amount early in the day. For narcolepsy, the usual daily dosage for adults ranges from 10 to 50 mg, preferably in divided amounts; for postencephalitic parkinsonism, the daily dosage is usually 10 to 25 mg, also in divided amounts. To control appetite in obesity, the usual daily dosage for adults is 15 to 30 mg in three divided doses, taken 30 to 60 minutes before meals. Light sleepers may take the final dose early (4 P.M.).

For children with behavior problems, the suggested dosage is 5 to 10 mg in the morning and 2.5 to 5 mg. at noon. In all cases, the dosage should be individualized; it is advisable to begin with an initial dose of 5 mg for adults or 2.5 mg. for children, followed by either one or two additional doses of the same amount. Dosage then can be increased to obtain the desired effect, the initial daily dose may be increased at first, leaving the repeated doses at the original level, so that the major quantity is taken during the first half of the day. If necessary, the later doses may be equalized gradually to provide a uniform action.

A capsule containing 10 or 15 mg of dextro amphetamine incorporated into variably coated pellets which afford continuous release of the drug over a period of 8 to 10 hours, thus prolonging the therapeutic effect for 10 to 12 hours, may be administered once daily in the morning to adults in place of ordinary oral medication in divided amounts.

SMITH, KLINE & FRENCH LABORATORIES

Elixir Dexedrine Sulfate: 355 cc bottles. An elixir containing 1 mg. of dextro amphetamine sulfate in each cubic centimeter.

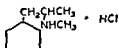
Powder Dexedrine Sulfate: 2.5 Gm. bottles

Spansule Sustained Release Capsules Dexedrine Sulfate: 10 and 15 mg.

Tablets Dexedrine Sulfate: 5 mg.

U S trademarks 373,000 and 590,757 (Spansule)

CYCLOPENTAMINE HYDROCHLORIDE,—**Clopans Hydrochloride** (LILLY).—N,α-1-Cyclopentyl-2-ethylammonium chloride
 tural formula of . . .
 as follows:



Physical Properties.—Cyclopentamine hydrochloride is a white, odorless, crystalline powder with a mild characteristic odor and a bitter taste. It melts between 113.0 and 116.0°. One part of cyclopentamine hydrochloride is soluble in 1.0 part of water, in 1.8 parts of alcohol, in 23.8 parts of benzene and in 1.3 parts of chloroform, and is slightly soluble in ether. The pH of a 1 per cent solution is about 6.2.

Actions and Uses.—Cyclopentamine hydrochloride has the actions and uses of sympathomimetic amines. It produces systemic pressor and local vasoconstrictor effects similar to those of ephedrine, but, unlike ephedrine, produces only slight cerebral excitation. Given orally it is more effective than ephedrine.

The drug is administered by injection as an adjunct to other measures for maintaining blood pressure in operative procedures and in types of cardiovascular collapse where sympathomimetic drugs are not contraindicated. It is useful also by topical application for the temporary relief of nasal congestion. Its local vasoconstrictor action does not appreciably interfere with ciliary movements.

Like other sympathomimetic agents, cyclopentamine hydrochloride should not be injected in patients with hyperthyroidism, and should be used with caution in patients with hypertension. Too frequent topical application also should be avoided to prevent such side effects as increased blood pressure, nervousness, nausea and dizziness, particularly in patients susceptible to vasoconstrictor agents.

Dosage.—As a nasal decongestant, a 0.5 per cent solution is applied topically by means of dropper, spray or tampon. Drops should be instilled with the head in the lateral head-low position; when stinging is encountered the solution may be diluted with isotonic sodium chloride solution.

A 1 per cent solution may be employed for office procedures or prescribed for use by patients who do not obtain adequate shrinkage with the 0.5 per cent concentration of the drug.

As a pressor agent to maintain blood pressure during spinal anesthesia or surgery, a dose of 25 mg. in 1 cc. of solution is recommended. It is injected intramuscularly just prior to administration of the anesthetic, with subsequent fractional doses as needed. To combat a rapid fall in blood pressure the drug may be administered intravenously, but by this route the drug must be injected very slowly and in doses not exceeding 5 to 10 mg. in order that the full effect of each dose may be determined.

ELI LILLY & COMPANY

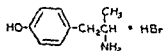
Solution Clopene Hydrochloride. 1 cc. ampuls. A solution containing 25 mg. of cyclopentamine hydrochloride in each cubic centimeter.

Topical Solution Clopene Hydrochloride 0.5%. 15 and 475 cc. and 3.78 liter bottles. An isotonic solution containing 5 mg. of cyclopentamine hydrochloride in each cubic centimeter. Preserved with phenylmercuric nitrate 1:50,000.

Solution Clopane Hydrochloride 1%: 30 and 475 cc. bottles. An isotonic solution containing 10 mg. of cyclopentamine hydrochloride in each cubic centimeter. Preserved with phenylmercuric nitrate 1:50,000.

HYDROXYAMPHETAMINE

Hydrobromide (SMITH, K.
phenol hydrobromide.—Th
amine hydrobromide may



Physical Properties.—Hydroxyamphetamine hydrobromide is a white, crystalline solid with a faint odor. It melts between 189 and 192°. It is very soluble in water, freely soluble in alcohol and practically insoluble in benzene and ether. A 2 per cent solution of hydroxyamphetamine hydrobromide has a pH between 4.5 and 5.5.

Actions and Uses.—Hydroxyamphetamine hydrobromide shares the general properties of other sympathomimetic amines. Studies with experimental animals indicate it to be somewhat less toxic than epinephrine and amphetamine. It produces little or no ephedrine-like central stimulation. Its principal therapeutic usefulness, therefore, is dependent on its peripheral effects. It is employed in solution for topical application to produce shrinkage of the nasal mucosa. For this purpose, at equal dosage levels, it is about twice as effective as ephedrine, in terms both of quickness and duration of action, and also less irritating. A 1 per cent solution of the drug instilled in the eye produces mydriasis suitable for ophthalmoscopic examination and, as an adjuvant to atropine and homatropine, helps in the induction of cycloplegia for refraction of adults and children, also promoting a rapid return of accommodation. By injection or by oral administration, the drug produces cardiovascular and intestinal effects similar, though not identical, to other sympathomimetic agents.

Dosage.—Hydroxyamphetamine hydrobromide is used in 1 per cent solution for topical application by instillation, tamponage or by atomized spray into the nostrils for shrinking of the nasal mucosa. The administration of 2 to 5 drops four to five times daily usually is sufficient for instillation. For sinus irrigation or displacement, the 1 per cent solution should be diluted with three parts of isotonic sodium chloride solution to make a 0.25 per cent solution of the drug.

A 1 per cent solution also is employed for instillation in the eye. For mydriasis, 1 or 2 drops are placed in the conjunctival sac. As an adjuvant for cycloplegia, 1 or 2 drops are instilled shortly after initial induction with 4 or 5 per cent solution of homatropine hydrobromide for adults, or a 1 per cent solution of atropine sulfate for children. Maximum cycloplegia is produced in 60 minutes. Full recovery in adults usually occurs the day after examina-

tion, and in children, the accommodative disability is reduced to 3 to 5 days.

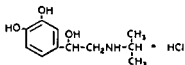
SMITH, KLINE & FRENCH LABORATORIES

Aqueous Solution Paredrine Hydrobromide: 30 and 360 cc. bottles. An aqueous solution containing 10 mg of hydroxyamphetamine hydrobromide in each cubic centimeter. Preserved with thimerosal 1.100,000

Ophthalmic Solution Paredrine Hydrobromide: 15 cc. dropper bottles. An aqueous solution containing 10 mg of hydroxyamphetamine hydrobromide in each cubic centimeter. Made isotonic with 20 mg of boric acid in each cubic centimeter Preserved with thimerosal 1.50,000.

U. S. patent 2,181,845. U. S. trademark 344,351.

ISOPROTERENOL
chloride (LILLY) —
Isopropylarterenol
tocatechuyl alcoho
isopropylaminoetha
isoproterenol hydrochloride may be represented as follows:



Physical Properties.—Isoproterenol hydrochloride is a white, odorless, slightly bitter, nonhygroscopic, crystalline solid. It melts between 166 and 172°. It is freely soluble in water, soluble in alcohol and very slightly soluble in benzene and ether. A 1 per cent solution of isoproterenol hydrochloride is clear and colorless, and has a pH between 4.5 and 5.5. Aqueous solutions of isoproterenol hydrochloride become pink upon standing.

Actions and Uses.—Isoproterenol is a sympathomimetic amine closely related in its actions to epinephrine and levarterenol. There are certain important differences, however. The action on the smooth muscle of blood vessels is much less pronounced than

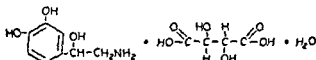
fleeting

Isoproterenol is a powerful cardiac accelerator and moderate dosage may produce an extreme tachycardia. The resultant cardiac insufficiency is characterized by precordial distress, palpitation, shock and electrocardiographic changes which suggest coronary insufficiency.

Preserved with 0.5 per cent chlorobutanol and 0.1 per cent sodium metabisulfite.

Sublingual Tablets Isonorin Sulfate: 10 mg. Each tablet contains 10 mg. of isoproterenol sulfate. Preserved with 0.5 per cent chlorobutanol and 0.1 per cent sodium metabisulfite.

LEVARTERENOL BITARTRATE-U.S.P.—*Levophed Bitartrate* (WINTHROP-STEARNs)—*l-α-(Aminomethyl)-3,4-dihydroxybenzyl alcohol d-bitartrate monohydrate.*—*l-Norepinephrine Bitartrate.*—The structural formula of levarterenol bitartrate may be represented as follows:



Physical Properties.—Levarterenol bitartrate is a white, crystalline, odorless powder. It melts between 100 and 106°. It is freely soluble in water, slightly soluble in alcohol and insoluble in ether. The pH of a 0.1 per cent solution is between 3.0 and 4.0.

Actions and Uses.—Levarterenol bitartrate, a water-soluble salt of the levo isomer of the primary pressor amine, arterenol, differs

slowing of the pulse rate of horizontal subjects and the absence of a stimulant effect on cardiac output. Levarterenol bitartrate produces a rise in blood pressure because it functions as a sympathetic mediator of peripheral vasoconstriction, whereas epinephrine acts as an over-all vasodilator and induces hypertension only by increasing cardiac output. In this respect, arterenol is similar to synthetic pressor amines, such as phenylephrine, which are preferred to epinephrine in the treatment of hypotensive states caused by central vasomotor failure and peripheral circulatory collapse. Levarterenol bitartrate produces about two and one-half times the effect of epinephrine on the blood pressure produced because

of blood pressure in acute hypotensive states caused by surgical and non-surgical trauma, central vasomotor depression and hemorrhage. It should not be employed for ordinary shock in place of appropriate intravascular fluids, such as plasma, when the fall in blood pressure is primarily the result of decreased blood volume rather than impaired vasomotor activity.

Levarterenol bitartrate is reported to have a safety ratio (pressor activity to toxicity) that is four times greater than that of epinephrine. Because of this and its lesser effect on the heart, levarterenol bitartrate is considered to be better tolerated and relatively safer than epinephrine. Infusion of levarterenol bitartrate may

produce a bradycardia, apparently of vagal origin, which is abolished by atropine. A few cases of transient headache and hypersensitivity have been observed following its use. Levarterenol bitartrate should be used with caution when cyclopropane anesthesia or other potentially cardiac-sensitizing agents are employed, because of the possibility of increasing the risk of ventricular fibrillation.

Levarterenol bitartrate appears to be useful also for adjunctive treatment in the management of hypotensive shock following myocardial infarction, particularly when the shock is not so severe that a blood pressure reading cannot be obtained. When a blood pressure reading cannot be obtained, other measures such as the intra-arterial infusion of blood or plasma may be employed initially, followed by levarterenol bitartrate in a dosage sufficient to keep the restored blood pressure above the shock level. Levarterenol

Dosage.—Levarterenol bitartrate is administered by intravenous infusion in 5 per cent dextrose in distilled water, or 5 per cent dextrose in saline solution. These fluids containing dextrose protect against significant loss of potency because of oxidation. Administration in saline solution alone is not recommended. Whole blood or plasma, if indicated to increase blood volume, should be

that will permit an accurate estimation of the rate of flow in

average dose ranges from 2 to 4 mcg of the base (0.5 to 1 cc. of the dilution) per minute.

The matter of dilution should be based upon clinical requirements of fluid volume. If large volumes of fluid (dextrose) are needed at a flow rate that would involve an excessive dose of

the time the drug is started until the desired level is obtained and every 5 minutes thereafter to avoid overdosage and dangerous hypertension. The rate of infusion must be watched constantly and the patient never should be left unattended while receiving the drug. Since subcutaneous extravasation of the solution may

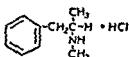
produce tissue necrosis, the needle or plastic tubing should be advanced well into the vein and secured in place.

WINTHROP-STEARNs, INC.

Solution Levophed Bitartrate 0.2%: 4 cc. ampuls. An isotonic solution containing 2 mg of levartercnol bitartrate in each cubic centimeter. Preserved with 0.2 per cent sodium bisulfite.

U. S. trademark 434,232.

METHAMPHETAMINE HYDROCHLORIDE-U.S.P.—Amphedroxyn Hydrochloride (LILLY).—Desoxyephedrine Hydrochloride (UPJOHN).—Desoxyn Hydrochloride (ABBOTT).—Dexovel Hydrochloride (VALE).—Doxyfed Hydrochloride (RAYMER).—Efroxine Hydrochloride (MALTBIE).—Norodin Hydrochloride (ENDO).—Semoxydrine Hydrochloride (MASSENCILL).—Syndrox Hydrochloride (MCNEIL).—Desoxyephedrine hydrochloride.—*d*-1-Phenyl-2-methylaminopropane hydrochloride.—The structural formula of methamphetamine hydrochloride may be represented as follows:



Physical Properties.—Methamphetamine hydrochloride occurs as white crystals or as a white, crystalline powder. It is odorless, and its water solution is acid to litmus paper. One gram of methamphetamine hydrochloride dissolves in 2 cc. of water, 3 cc. of alcohol and 5 cc. of chloroform, it is very slightly soluble in absolute ether.

Actions and Uses.—The actions of methamphetamine hydrochloride differ from those of amphetamine sulfate only in degree. The central stimulant effects of methamphetamine hydrochloride may be slightly greater and the circulatory action slightly less than those of amphetamine.

Methamphetamine hydrochloride may be used in the treatment of narcolepsy, in controlling oculogyric crises and various other manifestations of postencephalitic parkinsonism, as an adjunct in the treatment of alcoholism and in the treatment of certain depressive conditions, especially those characterized by apathy and psychomotor retardation. The drug may be administered intravenously as a cerebral stimulant to facilitate psychotherapeutic interviews with psychotic or neurotic patients. In emergencies it is administered intravenously as a cardiovascular stimulant; in barbiturate poisoning and also in acute alcoholism it is used as an analeptic.

Methamphetamine hydrochloride has been used as an adjunct in the treatment of obesity. It depresses the motility of the gastrointestinal tract and allays the sensation of hunger. It may assist some patients adhere to a strict dietary regime and also help those who are overeating in response to a depressive state.

Solutions of the drug may be administered by injection to sus-

damage.

Dosage.—Orally. The initial dose of methamphetamine hydrochloride is 25 mg daily; this may be increased to 25 to 50 mg two or three times daily if necessary. To avoid insomnia, the drug should not be administered after 4 P.M.; excessive dosage may also interfere with normal rest. In the event of signs of toxicity—restlessness, sleeplessness, headache, vertigo, palpitation and arrhythmia—the drug should be discontinued and a sedative administered.

Parenterally. In emergencies a solution containing 10 to 15 mg of methamphetamine hydrochloride may be administered slowly by intravenous injection. A second injection should follow only after 15 to 20 minutes or when the full effects of the first have been realized. For emergencies, the corresponding intramuscular dose is 15 to 30 mg. To sustain or prevent a fall in blood pressure during barbiturate, spinal or regional anesthesia, a dose of 20 mg is administered subcutaneously immediately prior to induction, and repeated as necessary during the operative procedure. A dose of 15 to 20 mg administered intravenously at a moderate rate is used to facilitate communication with psychiatric patients.

ABBOTT LABORATORIES

Elixir Desoxyn Hydrochloride: 473 cc. and 3.78 liter bottles. An elixir containing 0.66 mg of methamphetamine hydrochloride in each cubic centimeter.

Solution Desoxyn Hydrochloride: 1 cc. ampuls. A solution containing 20 mg. of methamphetamine hydrochloride in each cubic centimeter.

Tablets Desoxyn Hydrochloride: 2.5 and 5 mg

U. S. trademark 434,257.

BIORGANIC LABORATORIES, INC.

Powder Methamphetamine Hydrochloride: Bulk; for compounding or manufacturing use.

ENDO PRODUCTS, INC.

Powder Norodin Hydrochloride: 1, 5 and 10 Gm. vials.

Tablets Norodin Hydrochloride: 2.5 and 5 mg

ELI LILLY & COMPANY

Elixir Amphetroxyn Hydrochloride: 473 cc. and 3.78 liter bottles. A solution containing 0.62 mg of methamphetamine hydrochloride in each cubic centimeter.

Tablets Amphetroxyn Hydrochloride: 2.5 and 5 mg.

MALTBIE LABORATORIES DIVISION, WALLACE & TIERNAN, INC.

Elixir Efroxine Hydrochloride: 118.3 and 473 cc. and 3.78 liter bottles. An elixir containing 0.66 mg of methamphetamine hydrochloride in each cubic centimeter.

Tablets Efroxine Hydrochloride: 5 mg.

U. S. trademark 547,887.

S. E. MASSENGILL COMPANY

Tablets Semoxydrine Hydrochloride: 2.5, 5 and 7.5 mg.

U. S. trademark 538,256.

MCNEIL LABORATORIES, INC.

Elixir Syndrox Hydrochloride: 473 cc and 3.78 liter bottles. An elixir containing 0.67 mg. of methamphetamine hydrochloride in each cubic centimeter.

Tablets Syndrox Hydrochloride: 5 mg.

U. S. trademark 529,491.

RAYMER PHARMACAL COMPANY

Solution Doxyfed Hydrochloride: 473 cc. and 3.78 liter bottles. A flavored aqueous solution containing 1.5 mg. of methamphetamine hydrochloride in each cubic centimeter.

Tablets Doxyfed Hydrochloride: 2.5 and 5 mg.

REXALL DRUG COMPANY

Tablets Methamphetamine Hydrochloride: 2.5 and 5 mg.

THE UPJOHN COMPANY

Tablets Desoxyephedrine Hydrochloride: 5 mg.

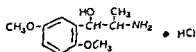
THE VALE CHEMICAL COMPANY, INC.

Tablets Dexoval Hydrochloride: 2.5 and 5 mg

THE WARREN-TEED PRODUCTS COMPANY

Tablets Methamphetamine Hydrochloride: 5 mg.

METHOXAMINE HYDROCHLORIDE-U.S.P.—Vasoxyl Hydrochloride (BURROUGHS WELLCOME).— β -Hydroxy- β -(2,5-dimethoxyphenyl)isopropylamine hydrochloride—The structural formula of methoxamine hydrochloride may be represented as follows:



pf 216^c Methoxamine hydrochloride is a white, bitter, odorless solid; it melts at 212 to 216°C. It is very slightly soluble in water, but is very slightly soluble in ether and ethyl acetate. In alcohol and chloroform it dissolves to form 100

cc of solution. The pH of the 2 per cent solution is 4.0 to 5.0.

Actions and Uses.—Methoxamine hydrochloride is a sympathomimetic amine compound which exhibits the vasopressor action (peripheral vasoconstriction) characteristic of other chemical agents of this class. Unlike the action of most pressor amines, the cardiac rate decreases as the blood pressure increases. This bradycardia, which is apparently caused by a carotid sinus reflex mediated by the vagus nerve, is abolished by atropine. Although the drug tends to slow the ventricular rate, it does not produce ventricular tachycardia, fibrillation or an increased sino-auricular rate nor does it increase the irritability of the cyclopropane-sensitized heart. Methoxamine also is free of cerebral-stimulating action. Tachyphylaxis has not been observed clinically.

Methoxamine hydrochloride is indicated primarily during surgery to maintain adequately or restore arterial blood pressure, especially in conjunction with spinal anesthesia, which tends to produce a fall in blood pressure. It is also useful as an adjunct in the treatment of hypotension associated with hemorrhage, trauma and surgery. Its adjunctive use is particularly indicated immediately after the induction of anesthesia in hypotensive patients.

shock

Like other vasopressor agents, methoxamine hydrochloride is contraindicated in patients with coronary disease. It should be used with caution in patients with cardiovascular disease. In patients with hypertension, the blood pressure during spinal anesthesia may be greater or more serious than in normotensive patients. Caution should be exercised to avoid overdosage resulting in high blood pressure and excessive bradycardia. High dosage occasionally may produce sustained, excessive blood pressure elevations with severe headache. Excessive dosage,

The usual intramuscular dose is 10 to 15 mg. When used to prevent a fall in blood pressure during spinal anesthesia, it is administered intramuscularly at the time of induction, and the dose is adjusted in accordance with the level of anesthesia to be employed, 10 mg may be adequate for operations below the level of the umbilicus, 15 to 20 mg for those above that level. A second dose should not be given until the previous one has had time to act, usually 15 minutes is sufficient. A solution of the drug containing 1 per cent procaine hydrochloride may be employed as the prophylactic intramuscular dose immediately prior to spinal anesthesia. From 0.1 to 0.2 cc. of such solution is used to make a skin wheal and produce local anesthesia at the site

selected for lumbar puncture. After inserting the needle deeper, the remainder of the solution needed to provide the pressor dose of the drug is injected intramuscularly. Lumbar puncture is then made through the skin wheal. In combating hypotension from other causes, the intramuscular dose is similar, but for pre-operative and postoperative use for moderate hypotension, 10 mg may be adequate.

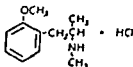
The usual intravenous dose, reserved for emergencies only, is 5 to 10 mg. administered slowly; however, the latter amount should not be exceeded. Intravenous injection may be accompanied by supplemental, intramuscular injection of 10 to 15 mg. to provide a more prolonged effect.

BURROUGHS WELLCOME & COMPANY, INC.

Solution Vasoxyd Hydrochloride: 1 cc. ampuls. A solution containing 20 mg. of methoxamine hydrochloride in each cubic centimeter.

Solution Vasoxyd Hydrochloride with Procaine Hydrochloride 1%: 1 cc. ampuls. A solution containing 20 mg. of methoxamine hydrochloride in each cubic centimeter and 10 mg. of procaine hydrochloride in each cubic centimeter.

METHOXYPHENAMINE HYDROCHLORIDE.—Orthoxine Hydrochloride (URJON).—2-(*o*-Methoxyphenyl) isopropylmethylamine hydrochloride.—The structural formula of methoxyphenamine hydrochloride may be represented as follows:



solution is between 5.3 and 5.7.

Actions and Uses.—Methoxyphenamine hydrochloride is a sympathomimetic compound whose predominate actions are bronchodilatation and inhibition of the smooth muscle. Its effect on blood vessels is minimal, its pressor activity being considerably less than that of ephedrine or epinephrine.

Methoxyphenamine hydrochloride counteracts smooth muscle spasm due to pilocarpine, histamine, acetylcholine and barium chloride. It is useful as a bronchodilator in the treatment of asthma and also is effective in allergic rhinitis, acute urticaria and gastro-intestinal allergy.

The usual doses of methoxyphenamine hydrochloride produce no alterations in blood pressure and only slight cardiac stimulation. The actions on the central nervous system are minor; some

patients become drowsy whereas others may be wakeful and nervous. Dryness of the mouth, nausea and faintness are less common side effects.

Dosage.—Adults, 50 to 100 mg., repeated every 3 or 4 hours if required. For children, a dose of 25 to 50 mg. is recommended.

THE UPJOHN COMPANY

Syrup Orthoxine Hydrochloride: 473 cc. bottles. A flavored syrup containing 10 mg. of methoxyphenamine hydrochloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben

Tablets Orthoxine Hydrochloride: 0.1 Gm.

U. S. trademark 509,060

METHYLHEXANEAMINE.—Forthane (Lilly).—1,3-Dimethylamylamine.—The structural formula of methylhexaneamine may be represented as follows:



Physical Properties.—Methylhexaneamine is a colorless to pale yellow liquid with an ammonialike odor. It boils between 130 and 135°. It is readily soluble in alcohol, chloroform, ether and dilute mineral acids and is very slightly soluble in water.

Actions and Uses.—Methylhexaneamine is a volatile sympathomimetic amine base, whose salts share the actions and uses of other vasoconstrictor agents. The systemic toxicity of methylhexaneamine in animals is greater than that of ephedrine and less than that of amphetamine. Its pressor action is more prolonged than that of epinephrine and is subject to tachyphylaxis, as shown by temporary tolerance of the peripheral arteries of animals to repeated injections. Soluble salts of the base produce mydriasis following local instillation.

When the inhaler is opened the volatile base is released and the drug is inhaled.

The drug is supplied in the form of a dry powder in a small container which is placed in the inhaler. The powder is released when the inhaler is opened and the drug is inhaled.

readily releases the volatile base when the inhaler is opened. This method of local application of the drug produces little or no effect upon the pulse rate or blood pressure of adult humans. If its use produces side effects such as headache, nervousness, mental stimulation or tremors, the drug should be discontinued.

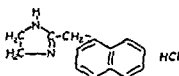
Dosage.—Methylhexaneamine is supplied in individual inhaler dispensers, each containing methylhexaneamine carbonate equivalent to 250 mg. of the base. One or two inhalations through each nostril is recommended as a single dose, to be repeated in accordance with the relief obtained at intervals of not less than one-half hour.

ELI LILLY & COMPANY

Inhaler Forthane: 250 mg. Each inhaler contains 250 mg. of methylhexanecamine and 32 mg. of menthol.

U. S. patents 2,350,318 and 2,386,273.

NAPHAZOLINE HYDROCHLORIDE-N.F.—*Privine Hydrochloride (CIBA).*—2-(1-Naphthylmethyl)imidazoline hydrochloride.—“Naphazoline Hydrochloride, dried at 105° for 2 hours, contains not less than 98 per cent of $C_{14}H_{14}N_2 \cdot HCl$.” *N.F.* The structural formula of naphazoline hydrochloride may be represented as follows:



Physical Properties.—Naphazoline hydrochloride occurs as a white, crystalline powder. It is odorless and has a bitter taste. Its solutions are neutral to litmus paper. It is freely soluble in water and alcohol, very slightly soluble in chloroform and practically insoluble in ether.

respiratory tract, such as nasal congestion of allergic and inflammatory origin, acute and chronic rhinitis, vasomotor rhinitis and acute and chronic rhinosinusitis. In acute nasal congestion, excessive use of vasoconstrictors may delay recovery. The rebound congestion of the mucosa sometimes caused by naphazoline hydrochloride can be alleviated within a few days simply by discontinuing all nasal medication. Those who respond with rebound congestion may tolerate solutions weaker than those commonly used. It is possible that the amount of drug absorbed following local application may be sufficient to increase the blood pressure. The drug also is useful as an ocular decongestant for symptomatic relief of bacterial, allergic and vernal conjunctivitis, to reduce blepharospasm and in the control of hyperemia of the palpebral and bulbar conjunctivae.

For ocular decongestion an isotonic solution containing 0.1 per cent is administered by the instillation of 1 to 3 drops in the conjunctival sac of the affected eye.

CIBA PHARMACEUTICAL PRODUCTS, INC.

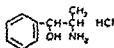
Nasal Jelly Privine Hydrochloride 0.05%: 20 Gm. tubes. Each gram contains naphazoline hydrochloride 0.5 mg. in a buffered water-soluble base containing glycerin, tragacanth and aromatics. Preserved with 0.01 mg thimerosal.

Solution Privine Hydrochloride 0.1% (Ophthalmic): 15 cc. dropper bottles. A buffered solution containing 1 mg. of naphazoline hydrochloride in each cubic centimeter. Preserved with 0.0065 per cent methylparaben and 0.0035 per cent propylparaben

Solution Privine Hydrochloride 0.1% (For Adults Only): 118 cc. bottles. A solution containing 1 mg of naphazoline hydrochloride, 2.6 mg of exsiccated sodium phosphate, 3.2 mg of sodium chloride, 2.2 mg of potassium chloride and 7.4 mg of potassium biphosphate in each cubic centimeter. Preserved with thimerosal 1:100,000.

Solution Privine Hydrochloride 0.05%: 15 cc nebulizers and 30 and 480 cc bottles. A solution containing 0.5 mg of naphazoline hydrochloride, 2.6 mg of exsiccated sodium phosphate, 3.3 mg of sodium chloride, 2.2 mg of potassium chloride and 7.4 mg. of potassium biphosphate in each cubic centimeter. Preserved with thimerosal 1:100,000

U. S. patent 2,161,938 U S trademark 398,804



Physical Properties—Phenylpropanolamine hydrochloride is a white crystalline powder with an odor like benzoic acid. Melting point between 190 and 194°. It is soluble in water and insoluble in benzene. Solutions are neutral to litmus.

ing action, phenylpropanolamine hydrochloride should be administered with caution to persons with heart or thyroid disease, high blood pressure or diabetes mellitus.

Dosage—As a local application, spray or instillation, 1 or 3 per cent aqueous solutions; orally in allergic conditions, 25 to 50 mg. three times daily usually is adequate for adults, with correspondingly smaller doses for children; to depress appetite in obesity, 50 mg. two or three times daily before meals for adults, 10 to 15 mg. three times daily for children 5 to 7 years of age, 25 mg. three times daily for children 8 to 12 years of age.

SHARP & DOHME, DIVISION OF MERCK & Co., INC.

Capsules Propadrine Hydrochloride: 25 and 50 mg.

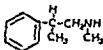
Elixir Propadrine Hydrochloride: 473 cc. and 3.78 liter bottles. A flavored elixir containing 4 mg. of phenylpropanolamine hydrochloride in each cubic centimeter

Solution Propadrine Hydrochloride 1%: 30 and 473 cc. bottles. An isotonic solution containing 10 mg. of phenylpropanolamine hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Solution Propadrine Hydrochloride 3%: 3.78 liter bottles. An isotonic solution containing 30 mg. of phenylpropanolamine hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

U. S. trademark 267,575.

PHENYLPROPYLMETHYLAMINE.—Vonedrine (MERRELL)—N,β-Dimethylphenethylamine—The structural formula of phenylpropylmethylamine may be represented as follows:



Physical Properties.—Phenylpropylmethylamine is a colorless to pale yellow liquid which begins to boil at 203° and 98 per cent of which distills between 205 and 210°. It is very soluble in alcohol, benzene and ether, and 12 parts dissolve in 100 parts of water. Aqueous solutions of phenylpropylmethylamine are alkaline to litmus; the pH of a solution of 2 drops (about 0.1 cc.) of phenylpropylmethylamine diluted with 10 cc. of water is about 10.5.

Actions and Uses.—Phenylpropylmethylamine base is volatile and, therefore, may be inhaled to produce nasal constriction. It produces little or no irritation, local tissue reaction or central nervous system and cardiovascular stimulation.

Dosage.—In using the phenylpropylmethylamine inhaler, one long inhalation through each nostril usually is sufficient. This may be

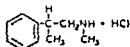
repeated as needed, although the usual care concerning such compounds should be exercised until more information is available in the entire field of sympathomimetic amine compounds, especially those used locally as nasal vasoconstrictors.

THE WM. S. MERRELL COMPANY

Inhaler Vonedrine: Each inhaler contains (at the time of manufacture) not less than 0.25 Gm. of phenylpropylmethylamine and aromatics.

U. S. patent 2,298,630 U. S. trademark 406,970.

PHENYLPROPYLMETHYLAMINE HYDROCHLORIDE.—*Vonedrine Hydrochloride* (MERRELL).—N,β-Dimethylphenethylamine hydrochloride.—Phenylpropylmethylamine hydrochloride is made by adding phenylpropylmethylamine to an aqueous solution of hydrochloric acid. It is not available in the dry state. The structural formula of phenylpropylmethylamine hydrochloride may be represented as follows.



Physical Properties.—The solution is clear, colorless and nearly odorless. It has a pH between 5.5 and 6.5.

dosage.

congestion

Phenylpropylmethylamine hydrochloride is incompatible with silver salts, tannates and picrates.

THE WM. S. MERRELL COMPANY

Solution Vonedrine Hydrochloride 2.8%: 30 cc. dropper bottles and 473 cc. bottles. A solution containing 28 mg. of phenylpropylmethylamine hydrochloride and 0.2 mg. of cetylpyridinium chloride in each cubic centimeter. Preserved with 0.05 per cent methylparaben and 0.01 per cent propylparaben.

U. S. patent 2,298,630. U. S. trademark 406,970.

PROPYLHEXEDRINE-U.S.P.—Benzedrex (SMITH, KLINE & FRENCH). — 1-Cyclohexyl-2-methylaminopropane. — "Propylhexedrine contains not less than 98 per cent and not more than 101 per cent of $C_{10}H_{21}N$." U.S.P. The structural formula of propylhexedrine may be represented as follows:



Physical Properties.—Propylhexedrine is a clear, colorless liquid with a characteristic amine odor. It boils between 202 and 206°. Propylhexedrine is very slightly soluble in water and soluble in dilute acids, alcohol and ether.

Actions and Uses.—Propylhexedrine is closely related to, and shares the actions and uses of, amphetamine and similar volatile sympathomimetic amine compounds. It produces vasoconstriction and a decongestant effect on the nasal mucous membranes. Propylhexedrine has only about one-half the pressor effect of amphetamine and produces decidedly less effect on the central nervous system. Propylhexedrine, therefore, is useful primarily for its local shrinking effect upon the nasal mucosa in the symptomatic relief of nasal congestion caused by the common cold, allergic rhinitis or sinusitis. Its volatility makes propylhexedrine convenient for intranasal application by inhalation and for reaching structures sometimes inaccessible to liquid forms of medication. Because of its wide margin of safety and relative freedom from toxic side effects, the use of propylhexedrine by inhalation is not contraindicated for patients in whom an ephedrine-like action would be undesirable. It is considered safe for self-medication by adults, but children should not have unsupervised access to an inhaler.

Dosage.—Propylhexedrine is administered by nasal inhalation with a portable inhaler containing 0.25 Gm. of the drug. The inhaler should be kept closed tightly between applications to avoid evaporation. The dose is two inhalations. If the dose may be repeated. If the patient is cold, it should be warmed in the hand before use because the volatility of propylhexedrine is reduced by cooling. With ordinary use, a 0.25 Gm. container will retain its effectiveness 2 to 3 months.

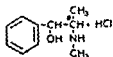
SMITH, KLINE & FRENCH LABORATORIES

Inhaler Benzedrex: Each inhaler contains 0.25 Gm. of propylhexedrine.

U. S. patent 2,454,746. U. S. trademarks 438,148 and 438,149.

RACEPHEDRINE HYDROCHLORIDE-N.F.—*Racemic* α -(1-methylaminoethyl)benzyl alcohol hydrochloride—*Racemic* Ephedrine Hydrochloride.—*dl*-Ephedrine Hydrochloride—"Racephedrine Hydrochloride, when dried at 105° for 3 hours, yields not less than

98.2 per cent and not more than 100.7 per cent of $C_{10}H_{15}NO \cdot HCl$ N.F. The structural formula of racephedrine hydrochloride may be represented as follows.



Physical Properties—Racephedrine hydrochloride occurs as fine white, odorless crystals or powder. It is affected by light. Its solutions are inactive optically. One gram of racephedrine hydrochloride dissolves in about 4 cc of water and in about 25 cc of alcohol. It is insoluble in ether.

Actions and Uses—Racephedrine hydrochloride produces peripheral effects similar to those of epinephrine. However, it is difficult to explain fully its effects without postulating some stimulation of the central nervous system and some action on striated muscle as well as direct stimulation of sympathetically innervated smooth muscle. In small doses, racephedrine hydrochloride stimulates the heart, increasing the rate and the strength of contractions and raising the blood pressure. In large and toxic doses the drug has a depressant action on the heart muscle. On intravenous or intramuscular injection it causes a rather lasting rise of blood pressure, due mainly to vasoconstriction. Other effects similar to those of epinephrine are dilatation of the bronchi and mydriasis after local or systemic administration. On local application to mucous mem-

of the eyes and to shrink the congested mucosa of the nostrils in rhinitis and sinusitis. It is useful in asthma, especially to prevent attacks, but often it fails partially or completely. It is used also in

3 to 4 hours.

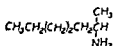
THE UPJOHN COMPANY

Capsules Racephedrine Hydrochloride. 25 mg.

Solution Racephedrine Hydrochloride 1%: A Ringer's solution

containing 10 mg. of racephedrine hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

TUAMINOHEPTANE.—Tuamine (LILLY).—1-Methylhexylamine—The structural formula of tuaminoheptane may be represented as follows.



Physical Properties.—Tuaminoheptane is a colorless to pale yellow liquid which boils between 138.5 and 142.5°. It is freely soluble in alcohol, benzene, chloroform and ether and is sparingly soluble in water. The pH of a 1 per cent solution is 11.45.

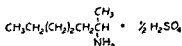
Actions and Uses.—This compound is a vasoconstrictor and a sympathomimetic amine. Inhalation of the vapors is an effective usefulness (see also
ld be used

Dosage.—An inhaler is available. The dosage is one or two gentle inhalations through each nostril, repeated at hourly intervals if necessary.

ELI LILLY & COMPANY

Inhaler Tuamine: Each inhaler contains (at the time of packing) the equivalent of 0.325 Gm. of tuaminoheptane and aromatics.

TUAMINOHEPTANE SULFATE.N.F.—Tuamine Sulfate (LILLY).—1-Methylhexylamine sulfate—"Tuaminoheptane Sulfate yields not less than 96.5 per cent of $\text{C}_{14}\text{H}_{31}\text{N}_2\cdot\text{H}_2\text{SO}_4$ " N.F. The structural formula of tuaminoheptane sulfate may be represented as follows:



Physical Properties.—Tuaminoheptane sulfate is a white, odorless powder, which is readily soluble in water. The pH of a 1 per cent solution is about 5.4.

Actions and Uses.—The vasoconstrictive effects of a 1 per cent solution of this compound exceed those of a similar concentration of ephedrine; 0.5 per cent solution produces about equal vasoconstrictor action. The duration of effect is greater than that of ephedrine.

Dosage.—A 1 per cent solution may be applied to the mucous membranes of infants and adults by spray, dropper or tampon and usually is adequate for routine treatment. A 2 per cent solution, best applied by pledgets of cotton, may be used for operative procedures, diagnostic examination and other special circumstances. For displacement therapy, a 0.2 per cent solution can be used.

ELI LILLY & COMPANY

Solution Tuamine Sulfate 1%: 30 and 475 cc. bottles. A solution containing 10 mg of tuaminoheptane sulfate, 6.8 mg of potassium phosphate monobasic and 0.9 mg of sodium chloride. Preserved with phenylmercuric nitrate 1:50,000.

Solution Tuamine Sulfate 2%: 60 and 475 cc. bottles. A solution containing 20 mg of tuaminoheptane sulfate and 6.8 mg of potassium phosphate monobasic. Preserved with phenylmercuric nitrate 1:50,000.

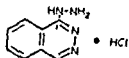
SYMPATHOLYTIC (ADRENERGIC BLOCKING) AGENTS

The effects of sympatholytic agents (antisympathomimetic) on the body resemble the effects of cutting the sympathetic (thoracolumbar visceral efferent) nerve supply. Such drugs are antagonists of epinephrine and, accordingly, often are referred to as adrenolytic agents. They slow the heart, lower blood pressure by extensive vasodilatation and increase gastro-intestinal muscle tone. Among the drugs that block the vasoconstricting and blood pressure elevating effects of epinephrine are ergotoxin, piperoxan and yohimbine. Ergotamine tartrate and F 883 diethylaminomethyl-1,4-benzodioxan more potently depress or block sympathetic reflexes. Various well-known preparations of ergot also exhibit this type of action in some degree; they are described in the chapter on oxytocics. Although a sympatholytic drug by strict definition must be adrenolytic, the reverse is not necessarily true. Certain drugs may be adrenolytic only, since the blocking of adrenergic drugs uniformly requires less potency or lower dosage than the blocking of sympathetic nerve stimulation.

Currently, the best known of these drugs are piperoxan, dibenzyl- β -chloroethylamine hydrochloride (Dibenamine Hydrochloride); tolazoline hydrochloride and phentolamine.

Clinical reports suggest that intravenously administered piperoxan reduces the blood pressure of patients having hypertension caused by circulating adrenalin from pheochromocytoma. Small intravenous, intramuscular or oral doses of phentolamine evidently similarly reduce blood pressure and aid diagnosis of pheochromocytoma. Dibenzyl- β -chloroethylamine (Dibenamine) administered intravenously blocks and reverses the pressor action of epinephrine and interrupts vasomotor reflexes for periods as long as 24 hours. Tolazoline hydrochloride and phentolamine are effectively administered orally in patients with certain circulatory disorders of the extremities, an action described as sympatholytic.

HYDRALAZINE HYDROCHLORIDE.—Apresoline Hydrochloride (Ciba).—1-Hydrazinophthalazine hydrochloride.—The structural formula of hydralazine hydrochloride may be represented as follows:



Physical Properties.—Hydralazine hydrochloride is a white, odorless, crystalline powder, with a melting point between 270 and 280° (with decomposition). It is very slightly soluble in ether. The amounts that dissolve in the following solvents to form 100 cc. of solution are 0.2 Gm. in alcohol and 4.4 Gm. in water. The pH of a 2 per cent solution is 3.5 to 4.5.

Actions and Uses.—Hydralazine hydrochloride, a derivative of phthalazine, is an antipressor drug that exerts chiefly a central

phorantasin and possibly other endogenous factors considered important in causing hypertension. Also, it inhibits the hormonal-cerebral vasopressor substance which may participate in varying degrees in more than one form of hypertensive disease and which is not affected by more potent adrenergic blocking agents. The capacity to inhibit a pressor substance of cerebral origin may explain the drug's effectiveness in neurogenic hypertension not benefited by extensive lumbar sympathectomy.

Hydralazine helps control essential and early malignant hypertension. Its efficacy often is greater in acute, more severe, non-terminal phases of these disorders. In advanced pathologic changes of the kidney (chronic renal hypertension or chronic glomerulonephritis), the effectiveness of the drug is diminished considerably. Although kidney function improves in some patients, evidence is lacking to indicate that the drug effects any anatomic alteration in patients with severe and progressive cardiovascular disease. More experience is necessary to determine whether the capacity of hydralazine to lower elevated pressure in early, severe hypertension will delay development of vascular damage. Worthwhile results may be expected in the toxemias of pregnancy. Preliminary studies indicate some beneficial effects in acute glomerulonephritis. Thus, hydralazine is a useful adjunct in the control of diverse forms of hypertension, with due consideration to the environmental, dietary and psychic factors involved.

Although true tolerance to the drug has not been demonstrated, blood pressure may rise occasionally during treatment. When this occurs, it may be advisable to discontinue therapy for a week, then resume, prescribing small doses as for initial treatment.

Because the toxicity of hydralazine is low, serious untoward effects seldom are encountered. Studies on experimental animals have not revealed evidence of chronic toxic effects on the tissues. Clinically, postural hypotension and circulatory collapse may precede a fall in blood pressure, but severe reactions of this kind are

relatively rare. The secondary effects of a reduction in blood pressure per se may cause tachycardia, headache, dizziness, faintness, palpitation, angina, numbness and tingling of extremities, malaise, depression, disorientation and anxiety. In addition to these side effects, the drug also may produce nausea, vomiting and mild periorbital, ankle, genital or other localized edema. Giant urticaria, relieved when the drug is withdrawn, also has been reported. In most patients, side effects usually disappear after the first 2 weeks of medication but may persist with continued therapy or reappear upon increase of the dosage.

The physician must be thoroughly familiar with the characteristics of hydralazine before prescribing or administering the drug. With such understanding on the maximal benefit, consistent with the use of the drug in the patient, the physician should be able to determine the dosage and the possible side effects.

acute systemic lupus erythematosus usually disappears when the drug is withdrawn or the dosage reduced. The severe erythematous form has been controlled with cortisone and corticotropin.

Dosage—Hydralazine hydrochloride usually is administered orally but may be injected parenterally (intramuscularly or intravenously) when the drug cannot be given by mouth. By either route, the dosage must be individualized in accordance with the response of the patient.

In the ambulatory patient, therapy should be initiated by the oral route, and the patient carefully instructed by the physician concerning the subjective effects that are produced. Headache and/or palpitation usually are experienced within 12 to 24 hours following the initial dose. These symptoms usually disappear spontaneously, with no change in dosage, within 7 to 10 days after starting treatment.

The initial dose for moderate to severe hypertension should be 10 mg, given four times daily, after each meal and at bedtime, to make a total daily dose of 40 mg. Individual doses should be spaced equally, and the total of 40 mg per day should be continued for the first 2 to 4 days, unless contraindicated because of severe or distressing side effects. The dose may be increased to 25 mg four times daily for the balance of the first week. During the second week, the dose may be increased to 30 mg four times daily (total daily dose of 200 mg). If side effects are absent or minimal and the blood pressure can be reduced to a more desirable level, the single dose may be augmented by 10 or 25 mg increments every 5 to 7 days. Most patients obtain maximal benefit from the schedule of 100 mg four times daily (total daily dose of 400 mg). However, some patients are stabilized best with as little as 100 mg per day in divided doses, others may tolerate as much

disease. Withdrawal of medication is not always necessary, and, when it is employed in other conditions, a reduction in dosage frequently is followed by a disappearance of untoward symptoms.

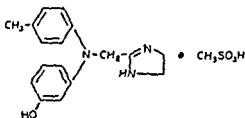
Dosage.—Phentolamine hydrochloride is administered orally. The usual adult dose is 50 mg. four to six times daily. Larger doses, as high as 100 mg., four to six times daily, may be necessary, especially in severer cases of peripheral vascular disease and hypertension. In children, the usual dosage is 25 mg. four to six times daily.

CIBA PHARMACEUTICAL PRODUCTS, INC.

Tablets Regitine Hydrochloride: 50 mg.

U. S. patent 2,503,059

PHENTOLAMINE *methanesulfonate* ($C_{17}H_{19}N_3O_4S$) (1-(2-methyl-5-(4-hydroxyphenyl)-1-imidazolyl)-2-phenyl-ethanesulfonate, dried at 60° in vacuum for 4 hours, contains not less than 98 per cent of $C_{17}H_{19}N_3O_4S$ U.S.P. The structural formula of phentolamine methanesulfonate may be represented as follows



Physical Properties—Phentolamine methanesulfonate is a white, odorless, bitter powder. It is freely soluble in water, very slightly soluble in acetone and practically insoluble in ethyl acetate. The amounts that dissolve in the following solvents to form 100 cc of solution are 6.8 Gm in alcohol and 0.15 Gm. in chloroform. Phentolamine methanesulfonate is stable when protected from moisture. The pH of the 1 per cent solution is 4.5 to 5.5.

Actions and Uses.—Phentolamine methanesulfonate, a water-soluble salt of the adrenergic blocking agent phentolamine, is used parenterally in the diagnosis and surgical management of hypertension caused by pheochromocytoma, a tumor that characteristically gives rise to excessive circulating epinephrine and/or levarterenol. Phentolamine, as the hydrochloride salt, is administered orally to pheochromocytoma and the mono-

graph on phentolamine hydrochloride

Phentolamine effectively blocks the pressor activity of epinephrine and levarterenol for longer periods and in smaller amounts than does piperoxan. Therefore, phentolamine methanesulfonate is considered more useful and less toxic than piperoxan as a diag-

nostic agent to exclude the presence of pheochromocytoma as a

doubt.

The use of phentolamine methanesulfonate as a diagnostic test for pheochromocytoma is based on its adrenolytic effect in producing a fall in blood pressure during a "typical" paroxysmal hypertensive episode. However, it is also indicated diagnostically in the presence of persistent chronic hypertension, especially when the hypertension is associated with a high basal metabolic rate, hyperglycemia and tachycardia, and in sudden severe hypertension in a normotensive or hypertensive patient during anesthesia or operative procedure and in hypertension in children or young adults, especially in the absence of severe renal disease. During the normotensive phase, that is, when the pheochromocytoma is not discharging sufficient epinephrine or levarterenol to elevate the blood pressure or to sustain an elevation, and in essential hypertension coexisting with a pheochromocytoma, repeated testing may be necessary to rule out "false negative" interpretation of a slight fall in blood pressure following administration of phentolamine.

A "false positive" drop in pressure may occur in patients with uremia and in those who have received sedatives prior to the test with phentolamine. Therefore, the test should be performed in the absence of sedation (or any anodyne) for at least 24 hours preceding. Basal blood pressure first is determined following a period of rest in the supine position, and the injection of the agent is delayed after introduction of the needle to allow the hypertensive effect of needle pain to subside.

The duration of the blood pressure response to phentolamine is influenced by the route of injection. Moderate or slight tachycardia is the only undesirable side effect of the test so far associated with intramuscular injection of the recommended dose. Given intravenously, the same dose has caused tachycardia with angina and, in rare instances, weakness, dizziness or flushing, none of which have been considered serious. The diagnostic and therapeutic use of phentolamine methanesulfonate in pheochromocytoma is considered to be relatively safe and free from alarming reactions.

Dosage—Phentolamine methanesulfonate is employed in permanently stable, lyophilized form for preparation of a fresh aqueous solution for administration by intramuscular or intravenous injection. In solution, phentolamine salts are stable for only about 6 months. For adults, the intramuscular or intravenous test dose is 5 mg in 1 cc of distilled water for injection, in children, an intramuscular dose of 3 mg or an intravenous dose of 1 mg usually is adequate. A typical positive response is characterized by an immediate drop in systolic and diastolic blood pressure. The maximum depressor effect usually is obtained within 2 minutes after intravenous injection and within 20 minutes after intramuscular injection. Generally, the systolic fall is approximately 60 mm Hg, with the diastolic fall exceeding 25 mm Hg, but the degree of response

may be somewhat less in some patients. After intramuscular injection, the reduction usually persists for some 30 minutes and gradually returns to previous levels within 3 to 4 hours. After intravenous administration, the blood pressure usually returns to previous levels within 10 to 15 minutes and, occasionally, within 2½ minutes. Negative responses are recorded when there is no change in blood pressure, a slight or moderate rise in blood pressure or only a slight lowering of blood pressure. The intravenous route should be employed if it is necessary to repeat the test to rule out false reactions.

In the control of blood pressure during surgical management of pheochromocytoma, the preoperative adult dose is 5 mg., intramuscularly or intravenously, 1 to 2 hours before the operation. This is repeated, if necessary, to prevent a paroxysm caused by anesthesia or emotional stress. For children, the preoperative dose is 3 mg. intramuscularly or 1 mg. intravenously. During operation, an intravenous dose of 5 mg. for adults or 1 mg. for children, repeated if necessary, may be given whenever blood pressure begins to rise as a result of stress or of manipulation of the tumor.

CIBA PHARMACEUTICAL PRODUCTS, INC.

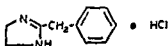
Lyophilized Regitine Methanesulfonate: 5 mg ampuls. Each ampul contains 5 mg. of phentolamine methanesulfonate. Packaged with 1 cc. vial of water for injection.

U. S. patent 2,503,059.

PIPEROXAN HYDROCHLORIDE.—See the monograph in the chapter on diagnostic aids.

TOLAZOLINE HYDROCHLORIDE USP Benzazoline Hydrochloride.—Benzazoline not less than 1 basis." U.S.P.

The structural formula of tolazoline hydrochloride may be represented as follows:



Physic white or slightly with a meltin alco- hol, chloroform and water and very slightly soluble in ethyl acetate. The pH of the 2.5 per cent solution is between 4.9 and 5.3.

. potent adreno- the transmis- it their recep- of circulating epinephrine and levarterenol. After blocking these sympathomimetic agents, the drug may cause "epinephrine reversal" by un-

masking their vasodilating component. Unlike other adrenolytic

therapy of peripheral ischemia and its resultant pain, loss of function, ulceration, gangrene and other trophic manifestations. It is useful in the treatment of a high percentage of patients with acrocyanosis, angitis obliterans, thrombo-vascular disease, sequelae of frost bite, roderma and ulcers of the extremities. Because the drug virtually abolishes normal vascular tone as well as neurogenic and humoral vasoconstriction in the extremities, it also can be employed as a diagnostic agent for the same purpose as sympathetic procaine block anesthesia, that is, to distinguish between functional (vasospastic) and organic (obstructive) components in occlusive peripheral vascular disease. The resultant increase in blood flow likewise provides an index of the initial vasospasm and the degree to which a decrease in normal vascular tone will augment blood flow in ischemic tissues; however, such information cannot be used to forejudge the possible

Although the drug has relatively low toxicity, its use is accompanied by various side effects. Flushing, goose flesh, formication

meals. Parasympathomimetic agents may be employed to counteract effects of the drug on the lower digestive tract. Intra-arterial administration is associated with a feeling of warmth or even a burning sensation throughout the treated limb. Minimal side effects of arterial injection include flushing and pilo-erection, transient postural vertigo and slight tachycardia; the first two effects are used as criteria for the most effective dosage by that route. A paradoxical further decrease in blood supply is observed rarely in gangrene, but usually this disappears with continued treatment or can be obviated by preliminary administration of histamine. Damage to diseased arteries or to periarterial tissues has not been

reported even with prolonged treatment by the intra-arterial route. Such treatment may be employed concomitantly with anticoagulant therapy when the latter is indicated.

The effectiveness of tolazoline is enhanced by keeping the patient warm. Exposure to a cold environment should be avoided during treatment since this may result in increased heat loss from vasodilation and further damage to involved tissues. Because the drug stimulates gastric secretion of hydrochloric acid, it should be administered with extreme caution to patients with a history of peptic ulcer or gastritis. The drug should be given cautiously to patients with coronary artery disease because of its variable hypo-

or parenterally by subcutaneous, intramuscular, intravenous or intra-arterial injection. The oral route, either alone or in conjunction with parenteral therapy, is preferred when prolonged treatment is necessary. The most effective dosage is reached at or just below the point when the skin becomes flushed and the patient experiences a feeling of chilliness; therefore, the dosage must be individualized and adjusted carefully in accordance with the optimal vasodilation and side effects. The usual initial oral dose for adults is 25 mg four to six times daily; this may be increased gradually to obtain the desired response. The usual parenteral dose

instances.

Intra-arterial injection should be carried out only by those experienced in the procedure, preferably in a hospital or clinic, and then usually only after the maximum benefit from administration of the drug by other routes has been tried. Injection is made into the femoral, brachial or radial artery. For adults, an initial test dose of 25 mg should be administered slowly for the first injection to determine the response of the individual patient. The subsequent average dose ranges from 50 to 75 mg, administered once or twice daily at the outset. This dosage may be reduced later to two or three times weekly to sustain improvement and may be employed in conjunction with oral therapy to maintain vasodilation between injections.

With continued therapy, a cumulative vasodilating effect has been observed, which may sustain blood flow in peripheral vessels at comparatively high levels. This effect is attributed to the promoting of the development of collateral circulation and reestablishment of functioning channels.

CIBA PHARMACEUTICAL PRODUCTS, INC.

Elixir *Priscoline Hydrochloride*: 473 cc. bottles. A flavored elixir

containing 6.25 mg. of tolazoline hydrochloride in each cubic centimeter.

Solution Priscoline Hydrochloride: 10 cc. vials. A solution containing 25 mg. of tolazoline hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Tablets Priscoline Hydrochloride: 25 mg
U. S. patent 2,161,938.

PARASYMPATHOMIMETIC (CHOLINERGIC) AGENTS

These agents are chiefly of two types. choline derivatives, which act similarly to acetylcholine, and cholinesterase inhibitors, which prevent the destruction of the endogenous acetylcholine.

The effects of parasympathomimetic agents on the body resemble those seen when parasympathetic nerves are stimulated electrically. The effect that has been studied most is the vagal inhibition of the heart. Pilocarpine, physostigmine and acetylcholine are classed as parasympathomimetic because they slow the heart in much the same way as does the application of tetanizing current to the peripheral end of the cut vagus nerve. Di-isopropylfluorophosphate surpasses physostigmine and neostigmine in its powerful and irreversible inhibition of cholinesterase. It produces, for instance, a prolonged miosis that may prove helpful in the treatment of glaucoma.

The typical parasympathetic effects, in addition to cardiac inhibition, are vasodilation in certain areas, miosis and increased

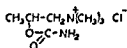
in many
is a very
t acts so
briefly because it is promptly rendered inactive by hydrolysis with

pathetic nerves, and is regularly kept from accumulating by the cholinesterase. Since physostigmine acts by opposing the cholinesterase, it is a parasympathomimetic drug; pilocarpine, muscarine and some others appear to act directly on the same receptive structure as does acetylcholine. Various choline derivatives have been synthesized that are sufficiently stable in the presence of cholinesterase to produce useful parasympathetic activity. Unlike acetylcholine, some are effective when administered orally and do not share its ganglionic action. Methacholine is perhaps the best example of this class.

Choline Derivatives

BETHANECHOL CHLORIDE—U.S.P.—Urecholine Chloride (SHARP

& DOHME).—Carbamylmethylcholine Chloride.—The structural formula of bethanechol chloride may be represented as follows:



Physical Properties.—Bethanechol chloride is a white, crystalline solid with an aminelike odor. It melts between 217 and 220° with decomposition. It is very soluble in water, freely soluble in alcohol and practically insoluble in chloroform, benzene and ether. The pH of a 0.5 per cent solution is between 5.5 and 6.3.

Actions and Uses.—Bethanechol chloride has pharmacologic properties similar to those of methacholine chloride but differs from acetylcholine in that it exhibits little if any ganglionic stimulating action and is not destroyed by cholinesterase. It is less toxic than some other esters of choline but is also less active.

Bethanechol chloride is useful in the treatment of conditions that are relieved by stimulation of the parasympathetic nervous system. It has been used successfully in the treatment of gastric retention following vagotomy, in postoperative urinary retention and in postoperative abdominal distention.

Although the drug has been tried in a number of other conditions that sometimes respond to parasympathetic stimulation, its precise role is not fully established. However, it may be tried in such disorders as megacolon, adynamic ileus accompanying severe trauma, acute infections or neurogenic disorders, neurogenic atony of the urinary bladder with retention; and gastric atony and retention following gastric surgery.

Dosage.—The optimum method of administration and the dosage must be determined for the individual. Mild or moderately severe disorders may respond to oral therapy, whereas severe maladies may require subcutaneous injection of the drug.

Oral doses of 10 to 30 mg. of bethanechol chloride three or four times daily meet most needs. The effect of the drug sometimes is apparent within 30 minutes.

The drug never should be given intravenously or intramuscularly. It may be administered *subcutaneously* to patients who do not respond to oral therapy or to those whose physical condition precludes it. The usual subcutaneous dose is 5 mg. (1 cc), although some patients respond satisfactorily to as little as 2.5 mg.

... dose be determined by giving this minute to minute to disturbing may be re-ous injection produce a satisfactory response, but such doses should be given only after adequate trial with doses of 2.5 to 5 mg. Unpleasant and occasionally severe side effects may occur following subcutaneous doses

of 5 to 10 mg. All effects of the drug can be abolished promptly by subcutaneous or intravenous injection of 0.6 mg. atropine sulfate.

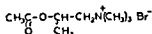
SHARP & DOHME, DIVISION OF MERCK & Co., INC.

Solution Urecholine Chloride: 1 cc ampuls. A solution containing 5 mg of bethanechol chloride in each cubic centimeter.

Tablets Urecholine Chloride: 5 mg.

U. S. trademark 389,037

METHACHOLINE BROMIDE.—Mecholyl Bromide (SHARP & DOHME) —(2-Hydroxypropyl)trimethylammonium bromide acetate—The structural formula of methacholine bromide may be represented as follows



Physical Properties.—Methacholine bromide is a white, crystalline very hygroscopic powder with a slight fishy odor. It melts between 146.5 and 148.5°. It is readily soluble in alcohol and water and insoluble in benzene and ether. The pH of a freshly prepared 5 per

other vasospastic conditions of the extremities, except possibly the management of vascular spasm from exposure to moderate cold.

Dosage.—Methacholine bromide is administered in doses of 0.2 to 0.6 Gm. two or three times daily, 50 mg. to 0.1 Gm. may be sufficient to overcome vascular spasm due to moderate exposure to

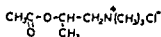
transfer (iontophoresis).

SHARP & DOHME, DIVISION OF MERCK & Co., INC.

Tablets Mecholyl Bromide: 0.2 Gm.

U. S. trademark 318,783

METHACHOLINE CHLORIDE-U.S.P.—Mecholyl Chloride (SHARP & DOHME) —Acetyl-β-methylcholine chloride—The structural formula of methacholine chloride may be represented as follows.



Physical Properties.—White crystals, or as a white crystalline powder, with a faint odor. It is very deliquescent. It is readily soluble in water, benzene and ether.

Actions and Uses.—Methacholine chloride is useful, by subcutaneous injection only, in the treatment of selected cases of paroxysmal auricular tachycardia not responding to the usual therapeutic measures. In the palliative local treatment of chronic rheumatoid (atrophic) arthritis it is used by the local method of ion transfer (iontophoresis) only. In the treatment of chronic ulcers, Raynaud's disease, scleroderma and other vasospastic conditions of the extremities it is used preferably by the local method of ion transfer (iontophoresis) but also by oral or subcutaneous administration when the electrical method cannot be employed. The drug is inferior to quinidine for the prevention of attacks of paroxysmal auricular tachycardia. It is of no apparent value in the treatment of other forms of tachycardia in auricular fibrillation, although there is a possibility of inducing transitory heart block, followed by resumption of normal rhythm. The drug is not useful in the treatment of bladder dysfunction, abdominal distention, atonic constipation, pelvic inflammation, functional dysmenorrhea, etc. (see the monograph

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due to moderate exposure to cold, oral doses of 50 mg. to 0.1 Gm. have been found effective. In Raynaud's disease, scleroderma and ulcers, the effective oral dose may be somewhat higher.

The subcutaneous dose should be limited to 10 mg. on the first injection to test the patient's tolerance. If tolerated, the dose may be increased cautiously up to 25 mg. This dose usually is adequate for injection when this method is employed in the treatment of Raynaud's disease, scleroderma, chronic ulcers and other vasospastic conditions of the extremities. In paroxysmal auricular

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abolished quickly by an injection of 0.6 mg. of atropine sulfate.

For application of methacholine chloride by the method of ion transfer (iontophoresis) it is customary to use a 1:200 to 1:500 solution of the drug in distilled water. The solution is applied by

moistening the positive electrode fabric that is placed over or near the part to be treated. The strength and duration of the galvanic current regulates the dosage and always should be applied gradually and within the amount comfortably tolerated by the patient. The patient should be instructed to report any sensation of excessive heat or burning. If this occurs, the treatment should be stopped and inspection made to determine if an electrode is improperly placed. The initial treatment should not exceed 5 to 10 ma. for 30 minutes. Subsequent treatments usually require from 25 to 30 ma applied for 20 to 30 minutes. When several parts are involved, each treatment should be restricted to a limited area such as one hand or one joint. Three or four days is the most satisfactory interval between treatments. The number of treatments necessary to obtain results varies with the patient and with the type of lesion. In Raynaud's disease and scleroderma, ten or more treatments may be necessary to secure improvement, in chronic rheumatoid arthritis the treatments may be reduced to intervals of a week after the first four to six treatments; in varicose indolent and gangrenous ulcers, treatments may be given daily at the start to promote granulation of tissue and then reduced after the first few treatments to two or three times a week. During treatments by ion transfer (iontophoresis) the patient should be covered and protected from drafts and for about 30 minutes after each treatment should be kept quiet and warm. He then may be permitted to resume protected activity.

Idiosyncrasy to methacholine chloride may result in difficulty in breathing. In this event treatment should be stopped and the patient raised to a sitting position. If untoward symptoms do not subside, atropine sulfate should be given at once hypodermically.

SHARP & DOWME, DIVISION OF MERCK & CO, INC

Powder Mecholyl Chloride: 1 and 10 Gm. bottles for the preparation of solutions for oral administration and for ion transfer (iontophoresis).

Powder Mecholyl Chloride: 25 mg ampul for the preparation of solutions for subcutaneous injection.

U. S. trademark 318,783.

Cholinesterase Inhibitors

The actions of acetylcholine are abolished when it is hydrolyzed by the specific enzyme, cholinesterase, the latter normally occurs in the serums and is distributed widely in the tissues, especially in nerve structures. This destruction is inhibited by a variety of substances, such as physostigmine, which thereby increase cholinergic (parasympathetic and ganglionic) activity. Other cholinesterases act more or less specifically on other choline esters.

arations are more stable. They are as active as physostigmine in stimulating intestinal peristalsis and have a similar but diminished *miotic* activity. There is no satisfactory evidence that the symptoms produced by toxic doses of benzpyrinium bromide or neostigmine salts are any less severe than those produced by comparable doses of physostigmine or its salts. This latter fact becomes especially important when it is considered that benzpyrinium bromide and neostigmine preparations are used by subcutaneous and intramuscular injection, since they are four to six times as toxic as physostigmine when injected subcutaneously in the rabbit. Atropine is the antidote to neostigmine.

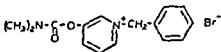
Neostigmine preparations and benzpyrinium bromide are used for the treatment of atony of the intestinal and bladder musculature and for the symptomatic control of myasthenia gravis. Their use for the treatment of intestinal and bladder atony is based on their vagotonic activity, because of their anticurarelike action, they are applied in the symptomatic treatment of myasthenia gravis. They are also credited with mild laxative action, but their use solely for that purpose is not advisable. The use of neostigmine methylsulfate has been recommended to antagonize the action of curariform drugs.

Neostigmine methylsulfate or benzpyrinium bromide is injected for the treatment of delayed menstruation and as a test for early

but also in the presence of organic systemic disease, endocrine disorders, etc., not associated with pregnancy. However, these drugs may be useful as a screening test for pregnancy; in the event of absence of bleeding following their administration the positive diagnosis of pregnancy should not be made until the result is checked by one of the acceptable biologic tests for pregnancy. They are recommended only for the induction of bleeding in temporary functional amenorrhea.

These agents are available only in the form of their salts.

BENZPYRINIUM BROMIDE.—Stigmonene Bromide (WARNER-CHILCOTT) —1-Benzyl-3-(dimethylcarbamoyloxy) pyridinium bromide.—The structural formula for benzpyrinium bromide may be represented as follows.



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tically insoluble in ether. A 1 per cent solution of benzpyrinium bromide has a pH between 4.5 and 5.5.

Actions and Uses—Benzpyrinium bromide has the same actions and uses as neostigmine. See the general statement on cholinesterase inhibitors.

Dosage.—For the treatment of postoperative abdominal distention, 1 cc. of the 1:500 solution (2 mg.) is administered by intramuscular injection, followed by a small, low enema 20 to 30 minutes after the injection. Intramuscular injection is repeated every 2 to 3 hours until the desired effect is obtained.

For the treatment of postoperative urinary retention, 1 cc. of the 1:500 solution (2 mg.) is administered by intramuscular injection, and heat (hot-water bottle, electric pad) is applied to the lower abdomen. The intramuscular injection is repeated every 2 to 3 hours until satisfactory micturition occurs or catheterization becomes necessary. In the latter instance, therapy should be continued until the patient voids spontaneously.

For the treatment of simple, delayed menstruation, 1 cc. doses of the 1:500 solution (2 mg.) are given by intramuscular injection once daily for 1 to 3 successive days. In the absence of endocrine disturbance, organic pelvic lesions or systemic disorders, menstrual flow may be evoked with the first or second injection, and further therapy third or fourth day.

As required when the 1:2,000 (0.5 mg.) solution is used, the former concentration has been found to be more convenient.

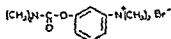
WARNER-CHILCOTT LABORATORIES, DIVISION OF WARNER-HUDNUT, INC.

Solution Stigmonene Bromide 1:500: 1 cc. ampuls. A buffered, saline solution containing 2 mg. of benzpyrinium bromide in each cubic centimeter.

Solution Stigmonene Bromide 1:2,000: 1 cc. ampuls. A solution containing 0.5 mg. of benzpyrinium bromide in each cubic centimeter.

U. S. patent 2,489, 247 U. S. trademark 557,370

NEOSTIGMINE BROMIDE—U.S.P.—Prostigmin Bromide (HORMANN-LA ROCHE)—3-Dimethylcarbamoylphenyl trimethylammonium bromide—"Neostigmine Bromide, dried at 105° for 3 hours, contains not less than 98 per cent of $C_{12}H_{18}BrN_2O_2$ " U.S.P. The structural formula of neostigmine bromide may be represented as follows.



Physical Properties—Neostigmine bromide is a white, crystalline

powder, odorless and of bitter taste. Its solutions are neutral to litmus paper. One gram of neostigmine bromide dissolves in about 1 cc. of water. It is soluble in alcohol and practically insoluble in ether.

Actions and Uses.—See the general statement on cholinesterase inhibitors. Neostigmine bromide is used orally for the treatment of myasthenia gravis. The bromide is used in the form of oral tablets as it is comparatively nonhygroscopic. It is also employed in an ophthalmic solution.

Dosage.—For π times a day after interval may be

Dosage should be kept at the minimum necessary to control symptoms without side effects. If more than 150 to 270 mg. per day is required, oral administration should be supplemented with neostigmine methylsulfate parenterally or with other drugs. Should unpleasant side effects occur, they often may be controlled with atropine sulfate.

A 5 per cent solution is used for ophthalmic instillation in the treatment of glaucoma, but in some cases half this strength may be adequate. Several drops usually are required as a single dose, and this should be repeated as often as necessary to maintain intraocular tension within normal limits.

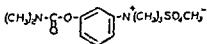
HOFFMANN-LA ROCHE, INC.

Ophthalmic Solution Prostigmin Bromide 5%: 7.5 cc. dropper bottles. A solution containing 50 mg. of neostigmine bromide in each cubic centimeter. Buffered with 1 per cent boric acid. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

Tablets Prostigmin Bromide: 0.015 Gm.

U. S. trademark 293,889 and 421,595.

NEOSTIGMINE METHYLSULFATE-U.S.P.—Prostigmin Methylsulfate (HOFFMANN-LA ROCHE)—3-Dimethylcarbamoylphenyl trimethylammonium methylsulfate.—“Neostigmine Methylsulfate, dried at 105° for 3 hours, contains not less than 98 per cent of $C_{13}H_{22}N_2O_6S$.” U.S.P. The structural formula of neostigmine methylsulfate may be represented as follows.



Physical Properties.—White, crystalline powder. It is neutral to litmus.

water. It is less soluble in alcohol at room temperature than in water. It melts between 140° and 145°.

Actions and Uses.—See the general statement on cholinesterase inhibitors.

Dosage.—Prevention of postoperative distention: Small doses of

the 1:4,000 solution are administered subcutaneously or intramuscularly at frequent intervals. Injections are begun as soon as possible and repeated in 1 cc. doses every 4 to 6 hours until the second or third postoperative day. Treatment of postoperative distention: Usually one or two ampuls of the 1:2,000 solution, as required, are administered subcutaneously or intramuscularly. Experimental use in the treatment of myasthenia gravis. Only one ampul
frequent
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treatment usually consists of one to four ampuls (0.5 to 2 mg. of neostigmine methylsulfate)

For induction of bleeding in temporary functional amenorrhea, 1 mg. (1 cc. of 1:1,000 solution) is injected daily for 3 successive days. If no bleeding occurs within 72 hours after the third injection, this is considered presumptive evidence of nonfunctional amenorrhea. In this case further efforts to induce bleeding should be abandoned until all nonfunctional causes are ruled out.

To combat the effects of overdosage of curariform drugs, 1 or 2 cc. of the 1:2,000 solution is used.

THE BOWMAN BROS. DRUG COMPANY

Solution Neostigmine Methylsulfate with Benzyl Alcohol 2%: 10 cc. vials. A solution containing 0.5 mg. of neostigmine methylsulfate in each cubic centimeter

HOFFMANN-LA ROCHE, INC.

Solution Prostigmine Methylsulfate 1:1,000 10 cc vials. A solution containing 1 mg. of neostigmine methylsulfate in each cubic centimeter. Preserved with 0.45 per cent phenol.

Solution Prostigmin Methylsulfate 1:2,000 and 1:4,000: 1 cc. ampuls
U. S. trademark 293,889 and 421,595.

LINCOLN LABORATORIES, INC.

Solution Neostigmine Methylsulfate 1:2,000. 10 cc. vials. A buffered, isotonic solution containing 0.5 mg. of neostigmine methylsulfate in each cubic centimeter. Preserved with 0.45 per cent phenol.

MEYER CHEMICAL COMPANY

Solution Neostigmine Methylsulfate 1:2,000. 1 cc. ampuls. A solution containing 0.5 mg. of neostigmine methylsulfate in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

E. S. MILLER LABORATORIES, INC.

Solution Neostigmine Methylsulfate 1:1,000: 10 cc vials. An isotonic solution containing 1 mg. of neostigmine methylsulfate in each cubic centimeter. Preserved with 0.02 per cent propylparaben and 0.18 per cent methylparaben.

Solution Neostigmine Methylsulfate 1:2,000. 1 cc. ampuls.

THE VITARINE COMPANY, INC.

Solution Neostigmine Methylsulfate: 5 cc. vials. A solution containing 1 mg. of neostigmine methylsulfate in each 1 cc. ampuls and 1 per cent methylparaben and 0.02 per cent propylparaben.

PARASYMPATHOLYTIC (CHOLINERGIC BLOCKING) AGENTS

The effects of parasympatholytic agents on the body resemble the effects of cutting the parasympathetic nerve supply to various parts. Drugs of the atropine-alkaloid series are classic members of this group. Atropine produces acceleration of the heart similar to that which occurs when both vagus nerves are cut, and causes dilatation of the pupil similar to that caused by cutting the oculomotor nerve. Some parasympatholytic drugs also reduce gastrointestinal motility and secretion.

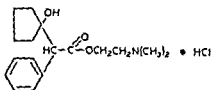
These drugs are antagonists to acetylcholine, which is liberated in ganglia and at cholinergic end organs. The enzyme cholinesterase also is found at nerve endings in the central, peripheral motor and parasympathetic nervous systems. This enzyme destroys acetylcholine and allows rapid repetitive impulse transmission by quickly hydrolyzing acetylcholine during each refractory period. Prostigmine accentuates the action of acetylcholine by inhibiting cholinesterase, and, therefore, is an antidote for some drugs of this series. Nicotine blocks both transmission of impulses and the action of acetylcholine. Certain newer anticholinergic drugs are curariform in nature in that toxic doses produce respiratory paralysis. Of these tetraethylammonium chloride when given intravenously or intramuscularly in moderate amounts blocks autonomic nerve transmission. Atropine, scopolamine, and the parasympatholytic drugs block the parasympathetic transmission. Each of these curariform drugs is also capable of blocking the intrinsic nerve plexuses of the intestinal tract, thus producing more complete inhibition of motility and secretion than occurs with atropine.

The usefulness of atropine is diminished by the fact that it affects so many organs simultaneously; on the eye in particular, its effects continue much longer than is often desirable. Many attempts have been made to secure drugs of the atropine type with more specific actions or drugs that have a more transitory effect upon the eye. One of these drugs is the tetraethylammonium chloride.

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CYCLOPENTOLATE HYDROCHLORIDE.—Cyclogyl Hydrochloride

ride (SCHIEFFELIN).— β -Dimethylaminoethyl (1-hydroxycyclopentyl)-phenylacetate hydrochloride.—The structural formula of cyclopentolate hydrochloride may be represented as follows:



Physical Properties.—Cyclopentolate hydrochloride is a white, odorless, crystalline solid, with a melting point between 137 and 141°. It is very soluble in water, freely soluble in alcohol and practically insoluble in ether. The pH of a 1 per cent solution is 5.0 to 5.4.

Actions and Uses.—Cyclopentolate hydrochloride, a synthetic spasmolytic agent, produces a rapid, intense cycloplegia and mydriasis of moderate duration when instilled in the eye. Therefore, it is useful primarily for refraction studies and is effective in highly pigmented irises as a substitute for atropine. It is also useful as a mydriatic in keratitis and choroiditis or in conjunction with ti breaking or preventing adhesions formed during and after infections. No significant variation of intra-ocular tension has been reported from its use, but it is considered advisable to neutralize any cycloplegic in older patients in whom early, unrecognized glaucomatous changes may be present.

Cyclopentolate hydrochloride in solution does not produce any undesirable local or systemic effects following repeated instillation.

intra-ocular pressure

Dosage.—Cyclopentolate hydrochloride is administered only in the form of ophthalmic solutions for instillation into the conjunctival sac. For refraction in Caucasians, a dose of 2 drops of a 0.5 per cent solution in each eye (each drop instilled at 5-minute intervals) for adults produces maximal cycloplegia in 30 to 60 minutes. Complete recovery occurs within 24 hours. The administration of 1 or 2 drops of 1 to 2 per cent pilocarpine nitrate reduces recovery time to 6 hours or less. In deeply pigmented eyes of dark-skinned persons, the 0.5 per cent solution produces cycloplegia in two-thirds of the cases. In children, cyclopentolate hydrochloride usually produces cycloplegia in 15 to 30 minutes. In adults, instillation of 2 drops of 0.5 per cent solution results in return of reading ability in 6 hours. For children, pre-

treatment with cyclopentolate on the day prior to examination usually is not necessary. Normally, 1 or 2 drops of a 0.5 or 1 per cent solution are instilled in each eye at the time of refraction, followed 10 minutes later by a second such application. This regimen will produce satisfactory cycloplegia in all but the most refractory cases. If pretreatment in such individuals seems desirable, 1 or 2 drops of 1 per cent cyclopentolate may be instilled the evening prior to examination. Only in children with extremely dark irises has pretreatment with atropine been occasionally necessary.

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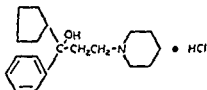
secondary to infections, 1 or 2 drops of a 0.5 per cent solution is instilled, followed in 6 hours by the instillation of 2 per cent pilocarpine nitrate. Such alternate treatment should be carried out every 24 hours.

SCHIEFFELIN & COMPANY

Ophthalmic Solution Cyclogyl Hydrochloride: 15 cc. bottles. A solution containing either 5 or 10 mg. of cyclopentolate hydrochloride in each cubic centimeter. Preserved with 0.002 per cent benzalkonium chloride.

U. S. patent 2,554,511

CYCRIMINE HYDROCHLORIDE.—*Pagitane Hydrochloride* (Lilly) — α -Cyclopentyl- α -phenyl-1-piperidinepropanol hydrochloride — Cyclopentyl-phenyl-3-(1-piperidyl)-1-propanol hydrochloride — The structural formula of cycrimine hydrochloride may be represented as follows:



Physical Properties.—Cycrimine hydrochloride is a white, odorless, bitter solid, with a melting point between 241 and 244° (with decomposition). It is practically insoluble in benzene and in ether. The approximate amounts that dissolve at 25° in the following solvents to form 100 cc. of solution are: 2 Gm. in alcohol, 3 Gm. in chloroform and 0.6 Gm. in water. The pH of a 0.5 per cent solution is between 4.9 and 5.4.

Actions and Uses.—Cycrimine hydrochloride is chemically related to the anticholinergics. In addition to the classical effects on the autonomic nervous system, it has been found to be effective in the treatment of Parkinson's disease. Studies in animals have shown that it acts as a parasympatholytic on smooth muscle, but

Compared with atropine, it has about one-half as much spasmolytic effect and about one-tenth as much antisialogogue effect. Likewise, it produces much less cardiovagal inhibition. The drug also has both mydriatic and ophthalmic anesthetic properties.

Cycrimine hydrochloride frequently is effective in the treatment of all three types of parkinsonism: postencephalitic, arteriosclerotic and idiopathic. The drug is effective more universally when the disease is based on postencephalitic etiology and less often effective when the condition is caused by arteriosclerotic changes.

In experimental animals, cycrimine hydrochloride is slightly more toxic than atropine. Its use should be avoided in conditions in which inhibition of the parasympathetic nervous system is undesirable. For example, it should probably not be administered in the presence of glaucoma and should be used with caution in the presence of tachycardia or any tendency toward urinary retention.

Clinically, the incidence and degree of side effects is chiefly a result of dosage. Side effects commonly observed include dryness of the mouth, blurring of vision, epigastric distress and transient nausea with anorexia. Since these effects may subside with continued therapy, discontinuance of the drug ordinarily is not required. Epigastric distress often can be overcome by administering medication with meals or with milk. More serious side effects, such as vertigo or disorientation, make it imperative to reduce the dosage or discontinue therapy entirely.

Dosage.—

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the arteriosclerotic type, likewise, do not tolerate large single doses. The dosage should be individualized and, when tolerance is poor, adequate total daily dosage often can be achieved with frequent administration of very small doses.

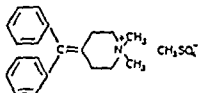
that is optimal from the standpoint of response and tolerance to side effects

ELI LILLY & COMPANY

Tablets Pagitane Hydrochloride: 1.25 and 2.5 mg

DIPHEMANIL METHYLSULFATE.—Prantal Methylsulfate (SCHER-

ING).—4-Diphenylmethylene-1,1-dimethylpiperidinium methyl sulfate — 4-Benzhydrylsdene-1,1-dimethylpiperidinium methylsulfate.
—The structural formula of diphemanil methylsulfate may be represented as follows:



Physical Properties.—Diphemanil methylsulfate is a white or near white, bitter crystalline solid with a faint characteristic odor and a melting point between 189 and 196°. It is very slightly soluble in ether. The approximate amounts that dissolve at 23° in the following solvents to form 100 cc of solution are, 3 Gm. in alcohol, 3 Gm. in chloroform and 3 Gm. in water. Diphemanil methylsulfate is stable to heat and light but is somewhat hygroscopic. The pH of a 1 per cent solution is between 4.0 and 6.0.

Actions and Uses.—Diphemanil methylsulfate is a quaternary parasympatholytic agent that selectively blocks the transmission of nerve impulses through parasympathetic ganglia. At the dosage level required to block parasympathetic ganglia, it does not block sympathetic ganglia. Diphemanil methylsulfate also inhibits gastric secretion and motility and relieves pylorospasm at a lower dosage than that required to inhibit motility of the small and large intestine. A slightly larger dosage effectively blocks cholinergic secretory nerve impulses to the sweat glands. The drug possesses considerable bronchodilator action, but further studies are required to establish its clinical usefulness in bronchial asthma.

Diphemanil methylsulfate is useful as an adjunct in the treatment of peptic ulcer, gastric hyperacidity and hypermotility as in chronic hypertrophic gastritis, in certain less specific forms of gastritis and in pylorospasm. It is not proposed for the control of spasm or hypermotility of the intestinal and the urinary tracts. The drug is effective for the treatment of hyperhidrosis and also for the control of sweating when this aggravates certain dermatoses.

Diphemanil methylsulfate is not absorbed readily from the gastro-intestinal tract, nor reabsorbed from the vascular system into the gastro-intestinal tract. Absorption by the oral route is reduced by the presence of food, antacids or bile salts in the stomach, but such interference largely can be obviated if the drug is administered between meals. Following parenteral injection, approximately 50 per cent of the drug is excreted unchanged, chiefly in the urine; the remaining 50 per cent has not been

found
diphemanil
affects in-
cluding xerostomia, mydriasis, tachycardia, constipation or diarrhea and urinary retention. Such reactions usually are minimal, but

they may interfere with therapy in some patients. As with other parasympathetic blocking agents, the drug usually is contraindicated in patients with glaucoma. An injectable solution of physostigmine methylsulfate may be administered in the usual adult dose of 2 mg. subcutaneously as an antidote to counteract the anticholinergic activity of diphehanil methylsulfate.

Dosage.—*Diphehanil methylsulfate* is administered orally and by subcutaneous or intramuscular injection. For the management

100 mg. Oral therapy also may be prescribed in the form of a coated tablet that prolongs the action of the drug over a period of 8 hours. In such form, 100 mg. administered at 8-hour intervals usually is adequate, but this may be increased to 200 mg. every 8 hours if necessary to maintain control of symptoms. When injected for initial control of symptoms or acute episodes, the usual dosage is 15 to 25 mg. administered subcutaneously or intramuscularly four times daily. If necessary, a dosage of 0.5 mg. per kilogram of body weight may be administered four times daily. A parenteral dose of 50 mg. should not be exceeded except with extreme caution. Injection of the drug preferably should be continued for 24 to 48 hours after symptoms are brought under control; thereafter, therapy should be continued by the oral route.

For the treatment of hyperhidrosis or control of sweating aggravating dermatoses, the usual oral dosage for adults is 100 to 200 mg. one to four times daily (between meals), prescribed either as ordinary or prolonged-acting tablets. Following inhibition, decreased dosage may be adequate to prevent recurrence.

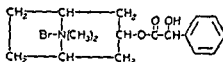
SCHIERING CORPORATION

Solution Prantal Methylsulfate: 10 cc. vials. A solution containing 25 mg. of diphehanil methylsulfate in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

Tablets Prantal Methylsulfate: 0.1 Gm.

Repetabs (Repeat Action Tablets) Prantal Methylsulfate: 0.1 Gm.
U. S. trademark 572,532

PHENAZOLINE METHYLPROPANE SULFONATE (Phenazone)



Physical Properties.—Homatropine methylbromide occurs as an odorless, white, crystalline powder having a bitter taste. It is affected by light. It dissolves in water and in alcohol but is insoluble in ether.

Actions and Uses.—Homatropine methylbromide is proposed for use in the treatment of gastro-intestinal spasm and hyperchlorhydria. Animal experimentation has shown it to be less active than atropine but also less toxic.

Dosage.—Adults. 2.5 to 5 mg three times daily before meals; children and infants, according to age.

CAMPBELL PHARMACEUTICAL COMPANY

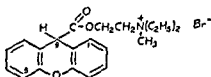
Tablets Novatrin: 2.5 mg.

ENDO PRODUCTS, INC.

Elixir Mesopin: 118.3 and 473 cc and 3.78 liter bottles. An elixir containing 0.5 mg of homatropine methylbromide in each cubic centimeter

Tablets Mesopin: 2.5 mg.

METHANTHELIN BROMIDE-U.S.P.—Banthine Bromide (SEARLE)
— β -Diethylaminoethyl-9-xanthenecarboxylate methobromide.—
“Methantheline Bromide contains not less than 98 per cent of $C_{21}H_{26}BrNO_3$, calculated on the anhydrous basis” *U.S.P.* The structural formula of methantheline bromide may be represented as follows.



Physical Properties.—Methantheline bromide is a white or nearly white, odorless, microcrystalline powder with a very bitter taste. It melts between 172 and 177°. It is very soluble in water, freely soluble in alcohol and practically insoluble in ether. A 2 per cent solution has a pH between 5.0 and 5.5.

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chloride. Toxic doses produce a curarelike action at the autonomic neuromuscular junction.

Like atropine, it produces mydriasis and cycloplegia when applied locally to the eye or administered systemically, but until more clinical evidence becomes available, its local use for this purpose is not recommended. The value of the drug for preventing abnormal cardiac reflexes through the vagus during thoracic surgery, or as an agent for routine preoperative medication in place of atropine, requires further investigation before final conclusions can be reached.

Methantheline bromide is indicated for clinical use whenever anticholinergic spasmolytic action is desired, provided it is not contraindicated because of its atropinelike characteristics or because of a patient's intolerance to the unavoidable side effects of

hidrosis or control of normal sweating that aggravates certain dermatoses and control of salivation.

Methantheline bromide produces some degree of cycloplegia and mydriasis in therapeutic doses and, therefore, should not be administered to patients with glaucoma. Sometimes it decreases the ability to read fine print. Xerostomia (dryness of the mouth) is a common, sometimes transient, side effect. Urinary retention of varying degrees may occur in elderly male patients with prostatic hypertrophy, and some patients may have difficulty emptying the rectum. Patients with edematous duodenal ulceration may experience nausea and vomiting during initial administration of the drug. These patients should take only liquids during the institution of drug therapy. All patients should be advised of the possible occurrence of side effects. Overdosage sufficient to produce a curarelike action may be counteracted by the prompt administration of oxygen and artificial respiration until the effects of the drug are exhausted.

Dosage.—Methantheline bromide is administered orally or parenterally by either the intramuscular or intravenous route. Parenteral administration is not advised for patients able to take the drug orally. The average initial dose for adults, oral or parenteral, is 50 mg. For patients with considerable intolerance, 25 mg. may be employed. In the management of peptic ulcer, a beginning schedule of 50 mg. three times daily before meals, and 100 to 150 mg. on retiring is suggested. However, the usual effective dose is 100 mg. four times daily, although some patients may require more or less than this amount. The dosage may be increased to tolerance, using dryness of the mouth as a guide, and adjusted to meet the individual response of patients. Maintenance dosage in peptic ulcer usually is considered to be about one-half the thera-

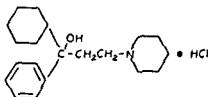
peutic level. In the management of other hypermotile or hypersecretory states, the dosage should be adjusted to the smallest amount that will relieve the symptoms. When spastic conditions are secondary to inflammatory or other organic lesions, therapy directed toward the cause should be employed whenever possible.

G. D. SEARLE & Co.

Powder Banthine Bromide: 2 cc ampuls. 50 mg.

Tablets Banthine Bromide: 50 mg.

U. S. trademark 537,763.



Physical Properties.—Trihexyphenidyl hydrochloride is a white, odorless solid, with a melting point between 249.0 to 249.5° (with slight decomposition). It is freely soluble in methanol and very slightly soluble in ether and in benzene. The approximate amounts that dissolve at 25° in the following solvents to form 100 cc. of solution are: 6 Gm. in alcohol, 5 Gm. in chloroform and 1 Gm. in water. The pH of a 1 per cent solution is 5.5 to 6.0.

Actions and Uses.—Trihexyphenidyl hydrochloride, a synthetic

of action on the cerebral motor centers. Unlike atropine, the action of trihexyphenidyl is strongest in producing desirable, relaxant side effects. Compared out one-half as intense mydriatic action, one-tenth as much cardio-

or the treatment of all ncephalitic, arteriosclerotic and idiopathic types. It reduces muscular rigidity and relieves the depression and mental inertia characteristic of this syndrome. The drug is especially effective in reducing the rigidity produced by muscle spasm, thus increasing the ability of the patient to achieve co-ordination of muscular motions. Tremor is

usually reduced, but in some patients who have been severely spastic, it may become more perceptible as spasticity is relieved. Sialorrhea is reduced but with less accompanying mouth dryness, blurred vision or mydriasis than with the use of atropine. Trihexyphenidyl is particularly useful in the treatment of arteriosclerotic parkinsonism because, unlike atropine, it usually does not tend to precipitate glaucoma.

Thus far, trihexyphenidyl hydrochloride has seldom produced

the drug. The infrequent but more severe reactions of mental confusion, agitation or nausea with vomiting tend to occur in arterio-

Dosage.—Trihexyphenidyl hydrochloride is administered orally. The usual initial dose is 1 mg. for the first day. If the patient is already receiving treatment with other agents, this initial dose should be substituted for a part of the current therapy. As the dosage of trihexyphenidyl is increased gradually, other medication should be decreased until the drug has replaced the former treatment or until an effective balance has been achieved. With prior therapy and in arteriosclerotic or sensitive patients, daily increments of the dose should be small until satisfactory tolerance is attained. If prior medication or unusual reactivity is not involved, the dosage is increased to 2 mg. for the second day, with subsequent increments of 2 mg. daily until a total daily amount of 6 to 10 mg. is reached. Postencephalitic patients may require as much as 12 to 15 mg. daily. At the lower level of daily dosage, the total amount can be divided into three equal parts, taken near meal times, at the higher level, a fourth dose at bedtime is required. Patients are allowed to choose whether to take the medication before or after meals. Postencephalitic patients, who have more excessive salivation, will prefer administration after meals and may require small doses of atropine sulfate as an adjuvant. Whenever the mouth becomes excessively dry, the drug can be taken before meals unless this causes nausea, if it is necessary to administer the dose after meals, dryness can be allayed by hard candy, gum or extra intake of fluid.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

Elixir Artano Hydrochloride: 473 cc. and 378 liter bottles. A flavored elixir containing 0.5 mg. of trihexyphenidyl hydrochloride

in each cubic centimeter. Preserved with 0.08 per cent methylparaben and 0.02 per cent propylparaben.

Tablets Artane Hydrochloride: 2 and 5 mg.

U. S. trademark 500,574.

GANGLIONIC BLOCKING AGENTS WITH BOTH PARASYMPATHOLYTIC AND SYMPATHOLYTIC ACTIONS

HEXAMETHONIUM BROMIDE and HEXAMETHONIUM CHLORIDE.—See the monographs in the chapter on cardiovascular agents

TETRAETHYLAMMONIUM CHLORIDE. — *Etamon Chloride* (PARKE, DAVIS) — Tetraethylammonium chloride is made in the form of a 50 per cent solution in water. From this solution, the dosage forms are prepared. The structural formula of tetraethylammonium chloride may be represented as follows:



Physical Properties.—Tetraethylammonium chloride, isolated by evaporating the 50 per cent solution in a vacuum, is an extremely hygroscopic, odorless, white solid. It is very soluble in water and in alcohol, freely soluble in chloroform and practically insoluble in benzene and in ether. The pH of the 50 per cent solution is 5.8 to 6.5.

Actions and Uses.—Tetraethylammonium chloride is a quaternary ammonium compound belonging to a class of drugs which, like nicotine and curare, act as generalized ganglionic blocking agents. The drug partially blocks transmission of motor nerve impulses through the ganglia of both the sympathetic and parasympathetic divisions of the autonomic nervous system. It is associated with vasospasm in the affected region, accompanied by reduction in arterial pressure resulting from vasodilation. The simultaneous interference with the transmission of parasympathetic impulses produces loss of ocular accommodation, cessation or decrease of motility of the gastrointestinal tract and alteration of urinary bladder function.

Tetraethylammonium chloride is of limited clinical usefulness as a therapeutic and diagnostic agent in the management of peripheral vascular disease, including intermittent claudication, Raynaud's disease, thromboangiitis obliterans, and frostbite. It is also used in the treatment of erythema gangrenosum, erysipelas, and other conditions of the foot and immersion foot. It may be employed diagnostically in cardiovascular conditions to estimate the contribution of sympathetic stimuli in the maintenance of vasospasm.

Tetraethylammonium chloride promptly lowers blood pressure in both normal and hypertensive patients. Peripheral circulatory

collapse has followed its use. Patients occasionally also experience

not be used in patients with recent coronary thrombosis and should be used with caution in all elderly patients and those with arteriosclerosis because they often experience unusual decrease in blood pressure with diminution in blood flow through the extremities.

Dosage—Tetraethylammonium chloride is administered by intravenous or intramuscular injection. Intramuscular injection produces local tenderness and burning. Subcutaneous injection produces considerable local irritation and oral administration is ineffective.

The intravenous dose is 2 to 5 cc. of a solution representing 0.2 to 0.5 Gm (not to exceed 7 mg per kilogram of body weight). The frequency of injection depends on the duration of the relief of symptoms. The effectiveness of the dose can be judged properly only on the basis of three or more injections. Injections may be given once or twice daily for several weeks in exceptional cases. The effects of the drug appear almost immediately following intravenous administration, and postural hypotension lasts from several minutes to 1 hour. Patients should be kept recumbent for at least 1 hour after intravenous injection.

36 hours in hospitalized patients. Continuation of the autonomic blockade for longer than 36 hours usually causes considerable distress. The addition of 1 cc of 2 per cent procaine hydrochloride solution to the dose of tetraethylammonium chloride decreases the discomfort caused by intramuscular injection.

Peripheral circulatory collapse should be treated by artificial respiration and/or injection of epinephrine hydrochloride solution 1:1,000. Intravenous administration of 0.5 to 1 mg. of neostigmine methylsulfate in solution antagonizes the blocking action of tetraethylammonium chloride and promotes rapid recovery from the postural hypotension.

PARKE, DAVIS & COMPANY

Solution Etamon Chloride 10%: 20 cc, Steri-Vials. A solution containing 0.1 Gm of tetraethylammonium chloride in each cubic centimeter. Preserved with 0.005 per cent benzethonium chloride.

U. S. trademark 432,476.

Blood Derivatives and Plasma Substitutes

Preserved whole blood and blood fractions generally are available to all physicians, either from blood banks, health departments or pharmaceutical houses.

Coagulation of whole blood and plasma is prevented by collecting the whole blood in sterile containers containing a pyrogen-free anticoagulant, an aqueous solution composed of citric acid, citrate and dextrose (ACD). Two standard ACD solutions are approved by the National Institutes of Health for use by licensed blood banks.

or fractionated into the several plasma protein products.

When blood is to be processed without delay into liquid or dried plasma or into plasma fractions, a pyrogen-free, aqueous solution of 4 per cent trisodium citrate may be employed as the anticoagulant. A final maximum concentration of 0.3 to 0.5 per cent of the citrate salt is recommended in both instances.

Preservation of whole blood requires constant refrigeration at 4 to 6°. The addition of dextrose to a blood preservative mixture significantly retards hemolysis of the erythrocytes and permits use of the blood for transfusion purposes for a period of 3 weeks. Even under adequate refrigeration, however, changes occur rapidly in the other cellular components, especially in the neutrophilic leukocytes and platelets, and more slowly in prothrombin and complement. Therefore, whole blood preserved in ACD solution should be used as soon as possible and in no event after the expiration of 21 days. Blood collected in plain sodium citrate, on the other hand, deteriorates much more rapidly and should be used within a 5-day period. Preservation of fresh plasma requires storage either in the frozen or dried state, while liquid plasma may be stored at room temperature for use in the treatment of shock.

Untoward reactions may follow the transfusion of whole blood, serum and plasma, but they rarely follow the use of plasma fractions. Inadequate blood grouping and crossmatching, errors in technique, circulatory overload, pyrogenic substances in the transfusion equipment, allergic idiosyncrasy and bacterial contamination may be responsible for reactions to whole blood. All but the first mentioned above may be responsible for reactions to

serum or plasma. Since heat readily coagulates and modifies the blood proteins, blood, plasma, serum or serum albumin should not be warmed prior to or during transfusion.

There are generally accepted medical criteria for the selection

transfusion donor. The following transfusible diseases are not -

jaundice, but such treatment of plasma or serum alters the structure of the proteins to varying degrees. Whenever plasma (or serum) is stored at room temperature for up to 2 years, it remains useful for the treatment of shock.

Whole blood is used for transfusion when it is desirable to administer the cellular blood elements and to supplement the diminished blood proteins. Either packed red cells or concentrated, compatible, blood cell suspensions in pyrogen-free, isotonic solutions can be used to replenish blood cell volume diminished by hemorrhage or blood dyscrasias when loss of red cells is the significant problem. However, it is important that transfusions of whole blood or of red cells be given only when truly indicated, since there is always some hazard of transmitting homologous serum jaundice.

The cell-free liquid portion of uncoagulated blood is plasma, while the fluid portion that remains when the cellular elements have been removed by coagulation is called serum. Blood plasma contains the three major blood proteins—albumin, globulin and fibrinogen, blood serum contains albumin and globulin only, the fibrinogen having been removed during the process of coagulation. Blood serum and plasma contain not only the proteins but also carbohydrates, fats, inorganic and organic salts, hormones, enzymes, vitamins and other soluble elements. Serum and plasma are used to restore diminished circulating blood volume in the treatment of shock and to supplement essential blood proteins lost through hemorrhage, burns, malnutrition and certain hemorrhagic blood dyscrasias. Both serum and plasma can be reduced by drying from the frozen state (lyophilization) to sterile dry powders that are reconstituted easily by the addition of sterile, pyrogen-free water. For plasma, a 0.1 per cent solution of citric acid is

used to avoid loss of the labile components, such as prothrombin and complement.

The blood plasma proteins—albumin, globulin and fibrinogen—can be separated by electrophoresis, ultracentrifugation and fractional precipitation by salts or organic solvents to yield highly purified products. In the fractionation of blood plasma, the standard method in wide use today is the cold-ethanol method developed during World War II. The protein fractions are not necessarily homogeneous as several different globulins (alpha, beta and gamma) have been isolated. Gamma globulin contains the greatest concentration of the antibodies used therapeutically or prophylactically for passive immunization against infectious diseases.

Therapeutic immune serums and serum derivatives currently licensed by the National Institutes of Health are: chicken pox immune serum, measles immune serum, mumps immune serum, pertussis immune serum, poliomyelitis immune serum, scarlet fever immune serum, poliomyelitis immune globulin and immune serum globulin (effective for measles and infectious hepatitis prophylaxis). The only difference between the two gamma globulin preparations mentioned last is that the poliomyelitis immune globulin has been tested for and found to contain a stipulated amount of antibody to the Lansing strain of the poliomyelitis virus. The immune globulin concentrate solution

administered only intramuscularly or subcutaneously, while the serums can be given intravenously as well. (See the chapter on immunologic agents for complete discussion.)

In addition to the gamma globulin fraction, the other useful protein fractions of plasma are fibrinogen (also processed into fibrin film and fibrin foam) and normal serum albumin. These products are also licensed by the National Institutes of Health. Fibrinogen contains antihemophilic globulin and is useful in the control of bleeding in hemophiliacs. Some evidence being accumulated indicates that this fraction also is useful in other types of uncontrolled bleeding due to unknown causes. Fibrin foam is prepared by mixing the fibrinogen with thrombin and beating it with air. The foam is used surgically to aid in the control of bleeding. Fibrin foam and therapeutic films have been used as a means of forming easily and by mixing, stable film is formed, are used particularly as a substitute for the dura mater in operations on the brain, as well as for some other procedures where this type of a preparation aids in surgical repair.

Blood grouping and typing reagents (serums), prepared from human blood, are essential for determining blood groups and types. The international classification (Landsteiner) of blood groups as O (universal donor), A, B and AB (universal recipient) is accepted widely and is used by blood banks all over the country. Specific

serums for determining the subgroups of A also are available, as are specific serums for some of the minor blood groups. The determination of the Rh type of the donor and of the recipient as either positive or negative has become routine in blood transfusion procedures, while the determination of specific Rh subtypes usually is carried out only when a question of isosensitization to one of the Rh factors is being investigated. Group specific

1. Diagnostic Serums

Anti-A Blood Grouping Serum

2. Anti-Rh Typing Serums

Anti-Rh₀ (Anti-D)

Anti-Rh₀' (Anti-CD)

Anti-Rh₀" (Anti-DE)

Anti-Rh₀ rh' rh" (Anti-CDE)

Anti-rh' (Anti-C)

Anti-rh" (Anti-E)

Anti-hr' (Anti-c)

Anti-hr" (Anti-e)

3. Others

Anti-K Serum (Anti-Kell)

Anti-Iy^a Serum (Anti-Duffy)

Anti-M Serum

Anti-N Serum

Blood Group Specific Substance A

Blood Group Specific Substance B

Blood Group Specific Substances A and B

For many years, dating back as far as World War I, there has been a continuous search for an acceptable and adequate "blood substitute." There is no substitute for whole blood, but research has developed some acceptable and satisfactory "plasma substitutes," also called plasma volume expanders. Many substances have been investigated for this purpose, including acacia, pectin and a number of synthetic chemical compounds. Most of these have proved to be either clinically inadequate or medically unsafe. This area of research has included investigation into the possibilities of purifying animal proteins as a substitute for human plasma. Thus far, it has not proved possible to despeciate such proteins sufficiently to avoid a possibility of sensitivity reactions of the anaphylactic type.

Two plasma substitutes currently are approved by the National Research Council and accepted by the Food and Drug Administration. These are gelatin and dextran. A refined 6 per cent solution

of gelatin (from beef bone collagen) provides a safe and clinically effective plasma substitute. However, this solution is a gel at room temperature and requires warming both before and during transfusion. This characteristic makes gelatin solution unsatisfactory for emergency field use. Dextran is the other approved plasma substitute and also is used as a 6 per cent solution. It is prepared by hydrolyzing sucrose with the bacterial organism *Leuconostoc mesenteroides* to produce a water-soluble, high molecular weight, glucose polymer. Some difficulty with mild to moderately severe allergic reactions has been encountered during the experimental work with this product, but this problem has been eliminated almost completely by refinements in the processing technique. It remains fluid to below freezing temperatures and, therefore, is the most satisfactory emergency plasma substitute available commercially. It is important to remember that both of these products, gelatin and dextran, as well as any of the other substances currently under investigation, are only temporarily effective in the severely injured patient, and whole blood (for burns, plasma or serum albumin also may be used) must be administered within 12 to 18 hours.

Other plasma substitutes under current investigation include polyvinylpyrrolidone (PVP), a high polymer product of the reaction, under high pressure, of formaldehyde, acetone, and a catalyst. It was used during World War II. It is stored in body form, for relatively long periods of time with a slow release.

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BLOOD DERIVATIVES

NORMAL HUMAN SERUM ALBUMIN. Normal Serum Albumin (Human).—Preparation of serum from healthy, human each 100 ml., 25 Gm. to 500 ml of normal human plasma, or a dried preparation suitable for restoration to an appropriate volume for clinical use. It contains no added bacteriostatic agent, but each 100 ml. of the liquid form may contain as a stabilizing agent either 0.04 mol of sodium acetyltryptophanate or 0.02 mol each of sodium acetyltryptophanate and sodium caprylate. If prepared from plasma containing a mercurial preservative, it contains not more than 20 mcg. of mercury per Gm. of albumin. Not less than 97 per cent of the total protein of Normal Human Serum Albumin is albumin. U.S.P.

Physical Properties.—Normal human serum albumin is a moderately viscous, clear, brownish liquid. It is substantially odorless.

Actions and Uses.—Normal human serum albumin is used to reduce edema and raise the serum protein level in hypoproteinemia; it is used also in the treatment of shock.

Dosage.—Approximately 2.2 cc. per kilogram of body weight is given at a rate not greater than 2 cc. per minute, usually accompanied by physiologic salt solution or 5 per cent glucose.

CUTTER LABORATORIES

Normal Human Serum Albumin (*Salt-Poor*) 25%: 20 and 50 cc. bottles, containing 5 Gm of albumin with not more than 0.33 per cent of sodium in a buffered diluent, osmotically equivalent to 100 cc. of plasma. No preservative added

Licensed by Research Corporation U. S. patent No. 2,390,074.

ANTIHEMOPHILIC PLASMA (HUMAN).—Irradiated antihemophilic plasma (human) is the sterile plasma prepared in a manner to prevent destruction of the relatively labile active fraction by pooling plasma obtained by centrifuging whole blood from approximately 20 donors. After sterilization by ultraviolet irradiation, the product is dried from a frozen state under high vacuum. The product meets the requirements of the National Institutes of Health of the United States Public Health Service.

Actions and Uses.—Antihemophilic plasma (human) is human plasma processed so as to prevent denaturation of the antihemophilic globulin component present in freshly prepared plasma. It is administered for the temporary reduction of the dysfunction of the hemostatic mechanism in hemophilia.

Dosage.—Antihemophilic plasma (human) is administered intravenously. It is employed as a solution, prepared by restoration of a freeze-dried preparation equivalent to either 60 or 120 cc. of citrated liquid plasma with either 25 to 50 or 50 to 100 cc of water for injection, depending on the volume to be used. Each 60 cc. equivalent of citrated liquid plasma, which is equivalent to 50 cc of original plasma or 100 cc of circulating whole blood, will maintain a normal clotting time for several hours to 2 days. This dose usually is sufficient for children; twice this amount may be required for adults. The maintenance dosage is dependent upon the weight and response of the patient. Injections should be repeated so as to maintain normal clotting time; repeated doses do not lose their effectiveness.

HYLAND LABORATORIES

Dried Antihemophilic Plasma (Human): 50 and 100 cc. bottles of plasma plus anticoagulant dried from the frozen state, packaged with 50 and 100 cc of 0.1 per cent citric acid diluent, respectively. The 50 cc size has built-in filter for administration by syringe; the 100 cc size is packaged with administration tubing, filter, needle adapter and intravenous needle.

IMMUNE SERUM GLOBULIN-U.S.P.—See the chapter on immunologic agents.

CUTTER LABORATORIES

Normal Human Plasma (*Dried*): Equivalent to 250 cc. restored plasma, packaged with 250 cc. of 0.1 per cent citric acid in distilled water as diluent.

HYLAND LABORATORIES

Normal Human Plasma (*Citrated*): Equivalent to 250 cc. pooled plasma containing 5 per cent dextrose.

Normal Human Plasma (*Dried*): Equivalent to 50, 250 and 500 cc., respectively, of restored plasma packaged with double-ended needle and 50, 250 and 500 cc. of 0.1 per cent citric acid in distilled water as diluent. The 50 cc. size has built-in filter for syringe administration, the 250 and 500 cc. sizes are packaged with or without administration tubing, filter and needle adapter.

MILWAUKEE BLOOD CENTER, INC.

Normal Human Plasma (*Citrated*): Equivalent to 250 cc. of pooled plasma containing 5 per cent dextrose.

MICHAEL REESE RESEARCH FOUNDATION

Normal Human Plasma (*Citrated*): Equivalent to 50, 250 and 500 cc. pooled plasma containing 5 per cent dextrose. The 250 cc. unit is provided either with or without an added 250 cc. of isotonic solution of sodium chloride.

Normal Human Plasma (*Dried*): Equivalent to 250 cc. of pooled original plasma packaged with a double pointed needle and 300 cc. of 0.1 per cent citric acid solution for restoration.

SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Lyovac Normal Human Plasma (*Dried*): 50, 250 and 500 cc. bottles of dried plasma, packaged with a double pointed needle and 50, 250 and 500 cc., respectively, of 0.1 per cent citric acid solution for restoration.

U S patent 2,176,004, U S. trademarks 357,061 and 380,366 (Lyovac).

NORMAL HUMAN SERUM.—Normal Human Serum is the

serum obtained by separating the plasma from whole blood of

normal human donors by centrifugation and removal of the

clot and the supernatant plasma is then separated from the

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and allowed to coagulate for at least 12 hours but not more than 24 hours. The cell-free serum is separated by centrifugation and transferred to a pool by means of a closed system. Sterility tests are made, a preservative is added, the serum is passed through a bacteria-excluding filter and distributed into the final containers through a closed system. *Caution:* Each lot of serum should be aged in the liquid state for at least 28 days at 2 to 10° subsequent to the removal of the clot and prior to its use as liquid serum, or

prior to freezing and drying. Normal Human Serum must be free from harmful substances detectable by animal inoculation and must not contain an excessive amount of preservative.

Actions, Uses and Dosage.—See the monograph on normal human plasma.

MICHAEL REESE RESEARCH FOUNDATION

Normal Human Serum: 20 and 250 cc. bottles.

PLASMA SUBSTITUTES

DEXTRAN. — **Expandex (COMMERCIAL SOLVENTS).** — **Gentran (BAXTER).** — **Plavolex (WYETH)** — Dextran is a water-soluble, high molecular weight glucose polymer produced by the action of *Leuconostoc mesenteroides* on sucrose. The marketed product has an average molecular weight of about 75,000.

Physical Properties.—Dextran is a white to light yellow, tasteless, odorless, amorphous solid. It is freely soluble in water. The powder is stable at room temperature.

Actions and Uses.—Dextran, when partially hydrolyzed to suitable viscosity and fractionated to provide an average molecular size of 75,000, is useful for intravenous administration in a 6 per cent solution of isotonic sodium chloride to expand plasma volume and maintain blood pressure in emergency treatment of hemorrhagic and traumatic shock. It should be regarded neither as a "substitute" for whole blood or its derivatives essential in restoring blood proteins nor for combating anemia secondary to hemorrhage or severe traumatic injury such as extensive burns and fracture.

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to 1,000 cc. of a 6 per cent solution usually persists 101 49 2000.

Dextran is excreted in the urine to the extent of 30 to 50 per cent, and studies in progress indicate that the remainder is metabolized in the body. Specific gravity of the urine is increased as a result of renal

has been elimin
of the 6 per c
perature, pulse
the period of

result of expanding plasma volume, venous pressure is raised from 10 to 30 mm. of water and cardiac output is elevated concurrently. Renal and hepatic functions are not altered by dextran.

Virtually no adverse reactions have been observed following repeated injections of dextran; however, this polysaccharide has the apparently inherent tendency to produce reactions of an antigen-antibody type in certain human subjects. Such reactions

are of low incidence and mild character in adequately hydrolyzed and refined preparations, which provide an average molecular size approximating that of serum albumin. As solutions of dextran do not require refrigeration, they are stored easily and are ready for immediate use in emergencies.

Dosage.—Dextran is administered intravenously as a 6 per cent solution in isotonic sodium chloride. The usual dose is 500 cc. infused at the rate of 20 to 40 cc. per minute, so that the total amount is administered over a period of about 15 to 30 minutes. Repeated injections may be given when necessary if blood or its derivatives are not available or suboptimally indicated. For human

ABBOTT LABORATORIES

Solution Dextran 6%: 250 and 500 cc. bottles. An isotonic solution containing 6 Gm. of dextran in each 100 cubic centimeters. The 500 cc. containers are available with or without Venoset (disposable venoclysis unit).

BAXTER LABORATORIES, INC.

Solution Gentran 6%: 250 and 500 cc. bottles. An isotonic solution containing 6 Gm. of dextran in each 100 cubic centimeters. The 500 cc. containers are available with or without sterile administration set.

COMMERCIAL SOLVENTS CORPORATION

Solution Expandex 6%: 250 and 500 cc. bottles. An isotonic solution containing 6 Gm. of dextran in each 100 cubic centimeters. The 500 cc. containers are available with or without a disposable syringe.

CUTTER LABORATORIES

Solution Dextran 6%: 250 and 500 cc. Saftiflasks. An isotonic solution containing 6 Gm. of dextran in each 100 cubic centimeters.

U. S. patents 2,089,217, 2,409,816 and 2,437,318.

HYLAND LABORATORIES

Solution Dextran 6%: 250 and 500 cc. bottles. An isotonic solution containing 6 Gm. of dextran in each 100 cubic centimeters. The 500 cc. containers are available with or without sterile administration set.

WYETH LABORATORIES, INC.

Solution Plavolex 6%: 500 cc. bottles. An isotonic solution containing 6 Gm. of dextran in each 100 cubic centimeters.

GELATINE SOLUTION, SPECIAL INTRAVENOUS.—A 6 per cent sterile, pyrogen-free, nonantigenic solution of gelatine in isotonic sodium chloride for use as an infusion colloid. The gelatine is prepared specially from refined beef bone collagen.

Physical Properties.—The gelatine solution is odorless, clear, amber-colored, and is stable at room temperature, but gels at 0°C. The solution is stable to the addition of 10% alcohol. The pH of the solution is between 6.95 and 7.40.

Actions and Uses.—Special intravenous gelatine solution is prepared specially for injection as a readily available infusion colloid to support blood volume in various types of shock. Thus, it is used as an osmotically effective substitute for plasma and whole blood when these substances are not indicated otherwise or are not available to meet emergency demands for restoring circulatory volume. In acute or recurrent hemorrhage or shock associated with loss of blood, whole blood is preferable to any substitute.

Special intravenous gelatine solution is excreted largely by the kidney and, therefore, should not be employed when there is renal impairment; it must be used with care in the presence of cardiac impairment to avoid the undue burden to the circulation of excessive fluid volume. Until further information is available it should not be used in the crush syndrome or in extensive third degree burns because these are associated with possible renal damage.

Since infused gelatine produces pseudoagglutination of the red blood cells, it should not be used in the treatment of hemorrhage.

Special intravenous gelatine solution is stable at room and refrigerator temperatures. It is completely fluid at body temperature and remains fluid after storage at 0°C. for 48 hours.

CHARLES B. KNOX GELATINE COMPANY, INC.

Special Intravenous Gelatine Solution 6%: 500 cc. bottles. A solution containing 6 Gm of gelatine in each 100 cubic centimeters.

AGENTS FOR BLOOD GROUPING

BLOOD GROUP SPECIFIC SUBSTANCES A AND B.—A sterile solution of polysaccharide-amino-acid complexes, capable of reducing the titer of the anti-A and anti-B isoagglutinins of group O donor blood. Blood group specific substance A is isolated as a precipitate from a tryptic digest of hog gastric mucin. Group specific substance B is isolated as a precipitate from a tryptic digest of the glandular portion of horse gastric mucosa.

Actions and Uses.—Blood group specific substances A and B, when added to group O blood, renders the latter reasonably safe for transfusions into patients having blood of another group. While this minimizes reaction attributable to the corresponding isoagglutinins, it should be kept in mind that group O blood may continue to give rise to reactions due to pyrogens, Rh incompatibility, immune anti-A or anti-B agglutinins and immunologic unknowns.

Dosage.—Blood group specific substances A and B may be added to group O blood just prior to administration or at the time of collection and storage. One transfusion unit (10 cc) is capable of reducing the anti-A and anti-B isoagglutinin titer of 500 cc. of group O blood to at least one-fourth of its original titer

SHARP & DOHME, DIVISION OF MERCK & Co., INC

Solution Blood Group Specific Substances A and B: 10 cc vials.
Preserved with 0.3 per cent phenol.

U. S. patent reissue No. 22,208.

Agents Affecting Blood Formation and Coagulation

Life is dependent upon a delicate balance within the blood itself and also within the walls of its container—namely the entire vascular system. Hemorrhage and thrombosis occur almost constantly in man and in other organisms, for the most part in minute areas. An imbalance in one direction resulting in a major thrombosis or in a hemorrhage may be disabling or fatal. The substances discussed in this chapter are designed to aid in the correction of such imbalance when it occurs either locally or generally throughout the system.

The substances having a purely local effect are for the most part directed toward acceleration of coagulation, such as the combating of hemorrhage, when applied directly to bleeding surfaces. These include thrombin, gelatin foam, fibrin foam, oxidized gauze and thromboplastic brain extracts. They are useful to combat oozing from minute vessels but should not be expected to control bleeding from arteries or veins when there is appreciable pressure at the bleeding point from within the bleeding vessel.

The substances having a general effect on this balance include several anticoagulants that decrease the tendency toward thrombosis. Of these, heparin was the first to be used successfully in man. It produces a prolongation of the clotting time as measured by the Lee-White method with a lesser effect on the prothrombin time. Heparin is used most commonly at present when a rapid effect is desired to prevent or control thrombo-embolic conditions. Its main disadvantage is its ineffectiveness when administered orally. The action of heparin is limited to a few hours, unless it is administered in a vehicle from which absorption and utilization are retarded.

Numerous compounds now are being developed that are effective orally and affect primarily the prothrombin activity and, in some instances, other clotting factors, such as factors V and VII. These include bishydroxycoumarin, cyclocoumarol, ethyl biscoum-acetate and phenindione. Their disadvantages include a much greater lag between administration and action than after the use

for hemorrhage in the event of overdosage or in the presence of pathologic conditions conducive to easy bleeding.

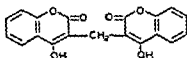
To combat excessive hypoprothrombinemia, water-soluble and

oil-soluble vitamin K preparations are used effectively. The latter are more potent and are highly effective when administered both parenterally and orally. Such preparations are discussed in the chapter on vitamins. This present chapter includes agents that influence the production of normal red corpuscles in the bone marrow and the quantity of iron held within them. These include dried stomach preparations which have been demonstrated to produce definite reticulocyte and red cell response. In general, these follow the type of response that has been obtained by active liver preparations given orally or parenterally. Stomach and liver preparations may be combined effectively. More recently, folic acid and cyanocobalamin have been found to be effective in the stimulation of red cell formation. A discussion of their actions will be found in the chapter on vitamins.

Ferrous sulfate is an effective agent for the treatment of iron deficiency anemias. It may produce diarrhea in some patients.

ANTICOAGULANTS

BISHYDROXYCOUMARIN—U.S.P.—Dicumarol. —3,3'-Methylenebis(4-hydroxycoumarin) —"Bishydroxycoumarin, dried at 105° for 3 hours, contains not less than 98 per cent of $C_{19}H_{12}O_6$ " U.S.P. The structural formula of bishydroxycoumarin may be represented as follows:



Physical Properties.—Bishydroxycoumarin is a white or creamy-white, crystalline powder. It has a faint, pleasant odor and a slightly bitter taste.

Actions and Uses.—Bishydroxycoumarin prolongs the prothrombin time by decreasing the prothrombin concentration of the blood. Although the exact mode of action is not known, it is assumed that bishydroxycoumarin acts on the liver to retard prothrombin production, since the circulating prothrombin present in blood is not affected *in vitro* by the addition of bishydroxycoumarin; the development of the bishydroxycoumarin effect requires 12 to 72 hours and persists for 24 to 96 or more hours after discontinuance of therapy.

Bishydroxycoumarin may be used in the prophylaxis and treatment of intravascular clots, postoperative thrombophlebitis, pulmonary embolism, acute embolic and thrombotic occlusion of peripheral arteries and recurrent idiopathic thrombophlebitis.

Bishydroxycoumarin does not directly affect thrombi or emboli already present nor does it increase the local blood supply of an area affected by an embolus. Bishydroxycoumarin retards further intravascular clotting and prevents propagation of the thrombus or embolus. In addition it permits dissolution of thrombi, presumably by the enzyme systems of the blood.

Since the ultimate outcome of acute coronary thrombosis depends largely upon extension of the clot and upon the formation of mural thrombi in the heart chambers with subsequent embolization, bishydroxycoumarin is used as an adjunct in the treatment of this condition. It is used widely now for the long-term prevention of embolization from mural thrombi which tend to form in the heart chambers in the presence of auricular fibrillation.

As with all coumarin derivatives, large doses of salicylates may enhance the action

Dosage.—Prothrombin clotting time should be determined every day during early stages of therapy. For long-term therapy, prothrombin clotting time tests should be performed once in 3 to 7 days. Until the time is 30 seconds, 200 to 300 mg. of bishydroxycoumarin is given each day. If it reaches between 30 and 35 seconds, dosage should be reduced to 50 to 100 mg. daily, and if it rises to 35 seconds or more, the drug should be withheld and not re-employed until the prothrombin time returns to 30 seconds or

(250 to 500 mg of vitamin K₁, orally) This treatment for hemorrhage may be supplemented by transfusions of fresh whole blood.

ABBOTT LABORATORIES

Tablets Dicumarol: 25 and 50 mg and 0.1 Gm.

ELI LILLY & COMPANY

Pulvules Dicumarol: 25 and 50 mg and 0.1 Gm.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

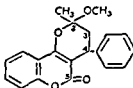
Capsules Dicumarol: 50 mg and 0.1 Gm.

THE UPJOHN COMPANY

Tablets Dicumarol: 0.1 Gm.

U S trademark 398,198 Dicumarol is the registered collective trademark of the Wisconsin Alumni Research Foundation which controls the use thereof

CYCLOCUMAROL.—Cumopyran (ABBOTT).—3,4-Dihydro-2-methoxy-2-methyl-4-phenyl-2H,5H-pyrano[3,2-c] [1]-benzopyran-5-one—The structural formula for cyclocoumarol may be represented as follows:



Physical Properties.—Cyclocoumarol is a white, crystalline powder

with a slight odor. It melts between 164 and 168°. It is insoluble in water and slightly soluble in alcohol.

Actions and Uses.—Cyclocoumarol, a synthetic anticoagulant related chemically and therapeutically to bishydroxycoumarin, produces its effect by lowering the blood concentration of prothrombin. It is useful, therefore, in the prophylaxis and treatment of intravascular clotting for the same purposes that have been recognized for other similar anticoagulants. See the monograph on bishydroxycoumarin.

equivalent amounts of other anticoagulants or that its use minimizes frequent variations in the prothrombin level, which may occur with shorter-acting anticoagulants

Cyclocoumarol is effective orally and should be administered with the same precautions observed for similar anticoagulants to avoid overdosage and hemorrhage. Little or no gastro-intestinal disturbance has been encountered with its use. Facilities should be available for making daily prothrombin determinations for the first stages of treatment and every 3 to 7 days for long-term therapy. For overdosage, blood transfusion and oral or parenteral administration of vitamin K should be used. Patients should be observed regularly for evidence of bleeding.

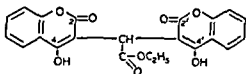
Dosage.—Initially, 0.1 to 0.2 Gm. is administered orally depending on the size and condition of the patient and the prior blood prothrombin level. Somewhat smaller doses usually are sufficient for patients with cardiac decompensation or myocardial infarction. The onset of effect usually occurs within 24 hours and the full therapeutic effect on prothrombin clotting time usually is reached within 36 hours.
anticoagulant effect,
institute therapy. At
determined daily for
to be administered a
than 35 seconds (control, 14 to 16 seconds), 12.5 to 50 mg. is administered daily. It is necessary to eliminate the drug on days when the prothrombin time exceeds 35 seconds.

ABBOTT LABORATORIES

Tablets Cumopyran; 50 mg

Manufactured by license from Wisconsin Alumni Research Foundation under U. S. patent 2,427,579 U. S. trademark 566,339.

ETHYL BISCOUMACETATE—Tromexan Ethyl Acetate (GELCO).—3,3'-Carboxymethylene bis-(4 hydroxycoumarin) ethyl ester.—The structural formula for ethyl biscoumacetate may be represented as follows.



Physical Properties.—Ethyl biscoumacetate is a white, odorless, bitter, crystalline solid which melts between 177 and 182°. Another form of the solid exists which melts between 154 and 157°. It is soluble in acetone and benzene, slightly soluble in alcohol and ether and insoluble in water.

Actions and Uses.—Ethyl biscoumacetate is a synthetic derivative of bishydroxycoumarin and similarly produces anticoagulant action by prolonging the prothrombin time through reduction of the prothrombin concentration of the blood. See the monograph on bishydroxycoumarin.

Ethyl biscoumacetate is effective orally, alone or as an adjunct to heparin sodium, for the prevention and treatment of conditions characterized or complicated by intravascular clotting. Compared

development of hemorrhagic complications. The drug is contraindicated in the presence of hemorrhagic diathesis and should be used with caution in patients with impaired hepatic or renal function.

Dosage.—1.5 Gm orally at once or in divided doses is recommended as the average adult dose for the initial 24-hour period of

usually require between 0.6 and 0.9 g as a therapeutic degree of hypocoagulation within 18 to 30 hours. A therapeutic level can be maintained by administering maintenance doses, such as 0.3 Gm. two or three times a day.

In patients with impaired hepatic or renal function, or in whom an exaggerated response is anticipated, a smaller than average initial dose is advisable. Following the initial dosage, maintenance doses should be regulated by the results of blood prothrombin determinations. When anticoagulant therapy is used in the hospital or for ambulatory patients, close supervision with frequent determinations of the prothrombin time is essential. For most purposes it is customary to prolong the prothrombin time to two or two and one-half times the normal. Daily determinations should be made during the first several days of treatment

each patient. Thereafter, the prothrombin time should be determined once or twice weekly. If the prothrombin time is less than 35 seconds are consumed, no further treatment is required. If the prothrombin time is exceeded, further treatment requires more

prompt anticoagulant effect than can be obtained by the use of

ethyl biscoumacetate alone, heparin sodium may be used to institute therapy.

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rhagic manifestations ensue, repeated transfusions of fresh, whole, citrated blood or plasma until the prothrombin level returns to a safe concentration. Elevation of prothrombin time to 75 seconds not associated with hemorrhage usually returns to a near normal range within 12 to 24 hours after prompt withdrawal of the drug only.

GEIGY PHARMACEUTICALS, DIVISION OF GEIGY CHEMICAL CORPORATION

Tablets Tromexan Ethyl Acetate: 0.15 and 0.3 Gm.

U. S. patents 2,482,510, 2,482,511 and 2,482,512

HEPARIN SODIUM-U.S.P.—Liquaemin Sodium (ORGANON).—
"Heparin Sodium is a mixture of active principles, having the
property of prolonging the clotting time of blood in man or other

less than 90 per cent and not more than 110 per cent of the potency stated on the label." U.S.P.

Physical Properties.—Heparin sodium is a white or pale-colored,

the thrombin.

Heparin sodium is of value as a substitute for citrate in blood transfusions, in attempts to prevent postoperative thrombosis and possibly thrombosis of other origin, to prevent recurring thrombosis in phlebitis and pulmonary embolism, to initiate the rapid action of anticoagulant therapy in vascular surgery and for other uses.

Dosage.—The potency of heparin sodium is expressed in terms of U.S.P. units because
potency is declared only
purification has been achieved
potency in terms of weight
in terms of the official units. Dosages stated below in terms of weight are based upon the U.S.P. minimum potency of 100 units per milligram.

The substance is inactive orally or sublingually and usually is injected intravenously or intramuscularly. It may be given by single

injection or continuous intravenous drip, the infusion being adjusted by watching the coagulation time. The clotting time should be maintained between 15 and 20 minutes. If a chill develops or spontaneous bleeding occurs, the drug should be stopped. When the interrupted dose method is employed, 5,000 units (50 mg) may be administered at intervals of 4 hours up to a total of 25,000 units (250 mg) per day. For continuous drip, 10,000 (100 mg) to 20,000 units (200 mg.) is added to 1,000 cc. of 5 per cent sterile dextrose or isotonic sodium chloride solution. The flow may be started at about 20 drops per minute.

Heparin sodium in aqueous solution also may be administered by intramuscular or deep subcutaneous injection, but the possibility of local hematoma or tissue irritation must be kept in mind. The possibility of concealed serious hemorrhage from accidental puncture of a blood vessel following deep injection into the tissues also should be kept in mind. This disadvantage can be minimized by administering the heparin subcutaneously with a hypodermic needle (25 or 26 gage) in more concentrated solutions. Solutions containing 5,000 units (50 mg), 10,000 units (100 mg.) or 20,000 units (200 mg) per cubic centimeter may be injected into the tissues in doses of 10, every 8 hours or 14,0 every 12 hours. Solution use without dilution.

Prolonged anticoagulant action of the drug is provided by deep subcutaneous or intramuscular injection of repository dosage forms prepared with a vehicle of gelatin and dextrose with and without added vasoconstrictors. Both forms are used simultaneously in equal amounts (except that when vasoconstrictors are contraindicated, only the latter is used) to provide a total initial dose of 0.3 to 0.4 Gm. of the drug, administered by deep subcutaneous injection in the thigh or buttocks. At the end of 12 hours, the

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ferred until clotting time is shorter than 20 minutes. In some patients this may be found to occur within 10 hours; in others, it may require 16 hours or longer. After a few such trials, the average response will be determined. It is always safest to determine the clotting time before more heparin sodium is administered. Maintenance of the blood coagulation time at 30 to 60 minutes is adequate elevation. As a rule, coagulation time should be not less than three times as great as it was at the start of therapy.

ABBOTT LABORATORIES

Solution Heparin Sodium: 10 cc vials. A solution containing 5,000 USP. units (approximately 50 mg) of heparin sodium in 1 per cent methylparaben.

Solution Heparin Sodium: 10 cc vials. A solution containing 5,000 USP. units (approximately 50 mg) of heparin sodium in

each cubic centimeter 5 cc. vials A solution containing 10,000 U.S.P. units (approximately 100 mg.) of heparin sodium in each cubic centimeter Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

ORGANON, INCORPORATED

Solution Liqueamin Sodium: 10 cc vials. A solution containing 1,000 U.S.P. units (approximately 10 mg.) of heparin sodium in each cubic centimeter Preserved with 0.45 per cent phenol.

Solution Liqueamin Sodium: 1 cc ampuls and 10 cc vials A solution containing 5,000 U.S.P. units (approximately 50 mg) of heparin sodium in each cubic centimeter Preserved with 0.45 per cent phenol

Solution Liqueamin Sodium. 4 cc vials A solution containing 10,000 U.S.P. units (approximately 100 mg) of heparin sodium in each cubic centimeter Preserved with 0.01 per cent thimerosal.

Solution Liqueamin Sodium: 2 cc vials A solution containing 20,000 U.S.P. units (approximately 200 mg) of heparin sodium in each cubic centimeter Preserved with 0.01 per cent thimerosal
U. S. trademark 361,309

PREMO PHARMACEUTICAL LABORATORIES, INC.

Solution Heparin Sodium 10 cc. vials. A solution containing 1,000 U.S.P. units (approximately 10 mg) of heparin sodium in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Solution Heparin Sodium: 10 cc vials A solution containing 5,000 U.S.P. units (approximately 50 mg.) of heparin sodium in each cubic centimeter Preserved with 0.45 per cent phenol.

TESTAGAR & COMPANY, INC.

Solution Heparin Sodium: 10 cc vials A solution containing 1,000 U.S.P. units (approximately 10 mg) of heparin sodium in each cubic centimeter Preserved with 0.5 per cent phenol.

Solution Heparin Sodium 10 cc vials A solution containing 5,000 U.S.P. units (approximately 50 mg) of heparin sodium in each cubic centimeter Preserved with 0.5 per cent phenol

Solution Heparin Sodium: 4 cc vials A solution containing 10,000 U.S.P. units (approximately 100 mg) of heparin sodium in each cubic centimeter Preserved with 0.5 per cent phenol.

THE UPJOHN COMPANY

Depo-Solution Heparin Sodium: 1 cc cartridges. A solution containing 20,000 U.S.P. units (approximately 200 mg) of heparin sodium in each cubic centimeter. Preserved with thimerosal 1:10,000

U. S. trademark 315,760 (Depo).

Solution Heparin Sodium: 10 cc. vials. A solution containing

1,000 U.S.P. units (approximately 10 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Solution Heparin Sodium: 4 cc. vials. A solution containing 10,000 U.S.P. units (approximately 100 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Solution Heparin Sodium: 1 cc. vials. A solution containing 20,000 U.S.P. units (approximately 200 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.4 per cent chlorobutanol.

THE VITARINE COMPANY, INC.

Solution Heparin Sodium: 10 cc. vials. A solution containing 1,000 U.S.P. units (approximately 10 mg.) or 5,000 U.S.P. units (approximately 50 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.5 per cent phenol.

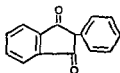
Solution Heparin Sodium: 4 cc. vials. A solution containing 10,000 U.S.P. units (approximately 100 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.5 per cent phenol.

WALKER LABORATORIES, INC.

Solution Heparin Sodium: 10 cc. vials. A solution containing 1,000 U.S.P. units (approximately 10 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Solution Heparin Sodium: 10 cc. vials. A solution containing 5,000 U.S.P. units (approximately 50 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.45 per cent phenol.

EFFELIN).—Medulin (WALKER).
structural formula of phenindione



Physical Properties.—Phenindione is a pale yellow, crystalline material. It is very slightly soluble in water. It is very slightly soluble in solvents to form Gm. in ether.

Action.—Phenindione is an anticoagulant, is similar in action to bishydroxycoumarin and its derivatives but is chemically unrelated. It is effective orally for lowering of the blood concentration of prothrombin in the management of conditions characterized or complicated by intravascular clotting (See the monographs on bishydroxycoumarin, cyclocoumarol and ethyl biscoumacetate).

Phenindione acts more promptly than does bishydroxycoumarin and is effective in smaller doses. Therapeutic levels usually are

agent is considered to be relatively safe. However, the predictability and controllability of its effect is not considered superior to other short-acting oral anticoagulants.

As with all systemic anticoagulants, the drug should not be given to patients with a hemorrhagic tendency, such as hemophilia, thrombocytopenic purpura and leukemia with pronounced bleeding tendency, or to patients with open wounds or ulcerations, particularly of the gastro-intestinal tract.

Dosage.—Phenindione is administered orally. The initial total daily dosage should be 0.2 to 0.3 Gm., half given in the morning and half at bedtime. Patients weighing less than 70 Kg. should be given 0.2 Gm. daily, those weighing more than 70 Kg. should receive 0.3 Gm. daily. Usually, this does not result in excessive

The maintenance dosage may vary from 0.03 to 0.1 Gm. per day, given in the same manner as the initial dose. The average maintenance dose is approximately 75 mg. When this has been established by daily prothrombin determinations for the first 3 days, the tests for prothrombin time need be repeated only at 7 to 14 day intervals or as may be indicated by the patient's response. If hemorrhage occurs, the drug should be withdrawn immediately and, when necessary, 50 to 75 mg. of vitamin K should be administered intravenously with or without transfusions of fresh whole blood or plasma.

GANZ'S CHEMICAL WORKS, INC.

Powder Phenindione: Bulk; for manufacturing use.

SCHIEFFELIN & COMPANY

Tablets Danilone: 50 mg.

WALKER LABORATORIES, INC.

Tablets Hedulin: 50 mg.

HEMOSTATICS

white, nonelastic, tough, porous matrix. It shows no tendency to

50 times its weight of water or 45 times its weight of well-agitated oxalated whole blood. Absorbable gelatin sponge will withstand dry heat at 149° for 4 hours.

It is used to control bleeding from wounds.

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completely in 4 to 6 weeks without inducing excessive formation of scar tissue or excessive cellular reaction. It is indicated in the control of capillary bleeding, particularly when moistened with thrombin solution.

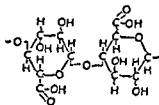
Dosage.—Absorbable gelatin sponge may be applied to the bleeding surfaces in amounts sufficient to cover the area. For such purposes it first should be moistened thoroughly with sterile isotonic sodium chloride solution or thrombin solution.

THE UPJOHN COMPANY

Sponge Gelfoam: Box of four sponges in individual envelopes and jars containing four sterile sections 20 by 60 mm., and sterile envelopes containing a single section 80 by 125 mm.

U. S. patent 2,465,357

OXIDIZED CELLULOSE-U.S.P.—Oxycel (PARKE, DAVIS).—Absorbable cotton or gauze.—Cellulosic acid—"Oxidized Cellulose, dried in a vacuum over phosphorous pentoxide for 18 hours, contains not less than 16 per cent and not more than 24 per cent of carboxyl groups (COOH)." U.S.P. The accepted structural formula for cellulosic acid may be represented as follows:



Physical Properties.—Oxidized cellulose, in the form of gauze or cotton, is almost white in color. It has an acid taste and a slight, charred odor. It is soluble in dilute alkalis but insoluble in acids and in water.

Actions and Uses.—Oxidized cellulose, a specially treated form of surgical gauze or cotton, exerts an unusual hemostatic effect and is absorbable when buried in the tissues. Its hemostatic action depends on the formation of an artificial clot by cellulosic acid. This acid has a marked affinity for hemoglobin, but does not enter per se into the physiologic mechanism of clotting. Absorbability depends on the size of the implant used, the adequacy of the blood supply to the area and the degree of chemical degradation of the material. Absorption of oxidized cellulose occurs between the sec-

ond and seventh day following implantation of the dry material, but complete absorption of large amounts of blood-soaked material may take 6 weeks or longer.

Oxidized cellulose is valuable in surgery for the control of moderate bleeding under conditions where suturing or ligation is technically impractical or ineffective. Such situations include the control of oozing from large or small arterial hemorrhage areas.

and in certain aspects of neurologic and otolaryngologic surgery. Oxidized gauze is employed as a sutured implant or temporary packing depending on the anatomic site or structures involved.

in severe cases, it is used for control of bleeding from the dura or brain tissue. This material likewise is useful as temporary packing for control of oozing from the dura or brain tissue. This material likewise is useful as temporary packing for control of oozing from the dura or brain tissue.

formation.

The hemostatic action of oxidized cellulose is not enhanced by the addition of other hemostatic agents. Thrombin would be destroyed by the low pH of the material and the hemostatic action of either alone is greater than that of the combination. Moistening with water or saline is not recommended, as the hemostatic effect is greater when the dry material is applied. When properly used, oxidized cellulose may be closed in a clean wound without drainage, but this is hazardous whenever gross contamination is suspected or frank infection is present.

Neither oxidized gauze nor oxidized cotton should be used as a surface dressing except for the immediate control of hemorrhage, as cellulosic acid inhibits epithelialization.

Dosage—The amount of oxidized gauze or cotton used varies with the circumstances. As a rule, only the minimal amount required to control hemorrhage should be used. For the control of hemorrhage from the prostatic bed, this may vary from one to four 2-in. by 14-in. gauze packing strips, depending upon the extent and vascularity of the area to be packed and the technic employed. This size of oxidized gauze is designed particularly for implantation by means of mattress sutures. Gauze packing strips $\frac{1}{2}$ in. by 2 $\frac{1}{2}$ in. are adapted for otolaryngologic or dental procedures; gauze packing 2 in. by 3 in. (4 ply) is used for severe postpartum uterine hemorrhage, cotton pads, 2 in. by 6 in., are designed for neurologic, oral and/or dental surgical procedures.

In the event that it is desired to remove gauze or cotton from a hollow viscus or drainage site before dissolution is complete, removal can be facilitated by irrigation. Discs of gauze may be

used in conjunction with hemostatic bags to control hemorrhage following suprapubic or retropubic prostatectomy.

PARKE, DAVIS & COMPANY

Oxycel Cotton Pledgets: $2\frac{1}{4}$ in. by 1 in. by 1 in. in a glass vial.

Oxycel Gauze Discs (*Foley Cones*) (4 ply): 5 in. and 7 in. each in a glass vial.

Oxycel Gauze Pads (8 ply): 3 in. by 3 in. in a glass vial.

Oxycel Gauze Strips (4 ply): 18 in. by 2 in. in a glass vial.

U. S. trademark 410,383.

THROMBIN-U.S.P.—"Thrombin is a sterile protein substance prepared from prothrombin of bovine origin through interaction with added thromboplastin in the presence of calcium. It is capable, without the addition of other substances, of causing the clotting of whole blood, plasma or a solution of fibrinogen. It may contain a suitable antibacterial agent." U.S.P.

Physical Properties.—Thrombin is a white or grayish, amorphous substance dried from the frozen state.

Actions and Uses.—Thrombin is intended as a hemostatic for topical application to control capillary bleeding in operative procedures. It may be applied as a dry powder or dissolved in sterile, isotonic saline solution *It should never be injected*

Dosage.—Thrombin is applied as a dry powder or in solutions containing 1,000 to 5,000 thrombin units.

PARKE, DAVIS & COMPANY

Thrombin Topical (*Bovine Origin*): Each vial contains 1,000 units of thrombin topical Preserved with 0.04 mg. of benzethonium chloride. Three vials packaged with one 6 cc. vial of isotonic sodium chloride diluent, preserved with benzethonium chloride 1.50,000.

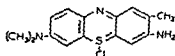
Thrombin Topical (*Bovine Origin*): 5,000 units. Each ampul contains 5,000 units of thrombin and sucrose, packaged with a 5 cc. vial of sterile isotonic saline solution preserved with 0.1 mg. of benzethonium chloride.

U. S. patent 2,398,077

THE UPJOHN COMPANY

Thrombin Topical (*Bovine Origin*): 30 cc. vials. Each vial contains 1,000 or 5,000 units of dried thrombin.

TOLONIUM CHLORIDE.—*Blutens Chloride* (ABBOTT).—3-Amino-7-dimethylamino-2-methylphenazothionium chloride—The structural formula of tolonium chloride may be represented as follows:



Physical Properties.—Tolonium chloride is a green, crystalline powder with a bronze luster. It is slightly soluble in alcohol, very slightly soluble in chloroform and practically insoluble in ether. The amount that dissolves at 25° in water to form 100 cc. of solution is about 5.5 Gm.

Actions and Uses.—Tolonium chloride, known as a dye by the name of toluidine blue O, exhibits *in vitro* antiheparin activity. In animals the coagulation times of blood samples known to contain an excess of heparin can be returned to normal by the addition of small amounts of the dye. Clinically, administration of the dye reduces hemorrhagic tendencies in hemophilic patients. It is also useful in the treatment of hemorrhoids. The dye can be detected by a protamine titration using protamine sulfate. A protamine sulfate titration value of 0.14 mg is considered the upper limit of normal.

Tolonium chloride is useful in the treatment of idiopathic functional uterine bleeding, menorrhagia or hypermenorrhea (abnormally profuse or prolonged menstruation) and menometrorrhagia (excessive or prolonged menstruation and intermenstrual bleeding). Approximately 80 per cent of patients with idiopathic uterine bleeding have elevated protamine titration values, and 75 to 80 per cent of the patients in this category respond to the dye. In patients treated empirically (not selected on the basis of elevated protamine values), the dye reduces bleeding in about 65 per cent. The mechanism of action has not been explained in uterine bleeding not associated with elevated protamine titration that responds to the dye. The dye should not be employed for the treatment of abnormal uterine bleeding until adequate examination and study have ruled out malignancy as the cause and, when so used without protamine titration, only if all other organic diseases have been ruled out.

Tolonium chloride has been demonstrated to have a low order of toxicity in experimental animals, no changes in coagulation time or capillary fragility have been observed. Extremely high doses injected into dogs produce hemolysis, leukocytosis and thrombosis, but these effects have not been encountered with therapeutic doses in man. Staining of internal organs may be apparent for a period of time following systemic administration of the dye, but no tissue damage has been attributed to this effect. The urine of patients receiving treatment becomes pale blue-green. Therapy also may be associated with such side effects as nausea, burning on urination and tenesmus, but these usually are absent or minor in importance in patients consuming adequate fluids. Since the side effects may respond to increased fluid intake, decreased dosage, or both, it rarely is necessary to discontinue therapy.

Dosage.—Tolonium chloride is administered orally. The usual dosage is between 0.2 and 0.3 Gm daily. For the treatment of menorrhagia, 0.2 to 0.3 Gm. is administered with meals during the menstrual period, for the prevention of menorrhagia, the same daily dosage is administered for 5 or 6 days prior to the estimated

time of the menses. In menometrorrhagia, medication may be extended over two or three menstrual periods.

ABBOTT LABORATORIES

Tablets *Blutene Chloride*: 100 mg.

U. S. trademark 587,379.

Cardiovascular Agents

Cardiovascular agents are those whose action on the heart and other muscular portions of the vascular system is such as to affect

The vasoconstrictor agents, such as epinephrine, will be found in the chapter on autonomic drugs, while ergot preparations are described in the chapter on oxytocics. A number of drugs with less definite vasodilator effects are described in other chapters; theobromine, caffeine and other xanthine derivatives in the chapter on diuretics, caffeine again in the chapter on central nervous system depressants and stimulants.

DIGITALIS AND RELATED PRINCIPLES

The digitalis group of substances consists of a number of glycosides, the most important of which are digitalin, digitoxin, and digitonin. They are all derived from the plant *Digitalis purpurea*.

All preparations of digitalis and related principles act directly on heart muscle. They diminish the size of the heart as measured

the heart rate by a combination of a direct action on the heart muscle and indirect inhibition by stimulation of the vagus. The larger the dose the more pronounced is the effect on the heart rate.

of the potent materials produce a systemic action, as shown by the fact that it requires only about one-fifth as much for intravenous as for oral administration to produce the same results. The potent principles of *strophanthus* are absorbed so poorly from the gastro-

intestinal tract that they are undesirable for oral administration and are used chiefly by intramuscular or intravenous injection in small doses.

Differences in Cumulative Action.—All the digitalis bodies in common use are cumulative in action. Not all show the same degree of cumulation, however, since some are more rapidly eliminated than others. The cumulative action is especially pronounced with *digitalis leaf* and *digitoxin*. It is much less with *strophanthus* and *strophanthin*. *Gitalin* (amorphous) is less cumulative than *digitoxin*, but more so than *digoxin*, *ouabain* and most tinctures of *digitalis*.

Differences in Emetic Action.—The digitalis principles are irritant to mucous membranes and subcutaneous tissues. Large doses produce in the gastro-intestinal tract the local irritation that may be sufficient to cause nausea and vomiting within several minutes to 1 or 2 hours. These drugs, however, rarely are administered in such doses, and when given in the usual smaller doses the local irritant action is insufficient to cause nausea or vomiting. The nausea or vomiting that follows the customary doses of digitalis

according to
over-

Standardization.—There are various methods for the standardization of this group of drugs, involving the use of several species of animals, such as the frog, guinea pig and pigeon. The *U. S. Pharmacopeia* requires that *digitalis* be standardized against the U.S.P. Digitalis Reference Standard by the official pigeon method which involves intravenous injection into pigeons until death occurs by cardiac arrest. The Standard preparation and the unknown are injected into groups of birds and the average fatal doses of the two are compared. The unknown then is adjusted so that 0.1 Gm. has the potency of 0.1 Gm. of the Standard, or 1 U.S.P. Digitalis Unit. Since the U.S.P. Digitalis Unit is the result of an assay by this method and represents an improved technic in bioassay, its use is preferable to direct testing of equivalent approximations of assay.

For *digitalis leaf* and tincture, the results of comparison by means of assays agree with similar comparisons in human beings to whom the drugs are given orally, but there is less agreement on purified materials because of wide differences in their absorption from the gastro-intestinal tract, and because the intravenous method does not distinguish absorbable from nonabsorbable material. Hence U.S.P. units of different specimens of the Digitalis

Leaf or Tincture Digitalis produce similar results when given orally to man (although there are some exceptions), but U.S.P. units of purified materials do not

greater clinical effect from these preparations than from crude digitalis preparations of equal strength.

Digitalis and digitalislike principles may be administered by mouth, by injection or as described under the accepted preparations. The *U. S. Pharmacopeia* recognizes a solution of digitalis for injection, but the optimum frequency of the intravenous dose

intravenous use of digitalis seldom is needed; other means of administration generally are safer and equally effective.

Research.—The disadvantages of all the drugs of the digitalis group have served as a constant stimulus in the search for pure principles suitable for intramuscular or intravenous administration. Pure principles would obviate the necessity of biologic standardization. A potent principle that is absorbed completely from

tions, such as digimon or digalen, however, are mixtures of glycosidal materials.

Proprietary Digitalis Preparations.—Several digitalis preparations

DIGILANID.—A mixture of the isomorphous crystallized cardio-active glycosides, lanatoside-A ($C_{49}H_{76}O_{19}$), lanatoside-B

having a hydroxyl group attached to carbon atoms 16 and 12, respectively.



Physical Properties.—The air-dried mixture is a white, odorless powder with a bitter taste. When heated rapidly, this preparation melts with decomposition above 245°. It is soluble in 20 parts of methanol and in 10,000 parts of water and is insoluble in ether.

Actions and Uses.—The actions and uses are closely similar to those of digitalis. (See the general statement on digitalis and related principles.)

Dosage.—The usual method of treatment is to give 0.67 to 1.33 mg. daily in tablet form, until the desired therapeutic effects are induced. The dose then is reduced to the maintenance level: 0.33 to 0.67 mg. daily in tablet form. (When digitalis effects are needed urgently, it may be desirable to initiate treatment with larger oral doses or with intramuscular or intravenous injections.) For rapid parenteral digitalization, 0.8 mg. (4 cc.) by cautious intravenous injection, or 0.4 mg. (2 cc.) twice daily by intramuscular injection. Rectally, 0.5 to 1 mg. (1 or 2 suppositories) daily, as required.

The same precautions should be observed as when giving any digitalis preparation.

SANDOZ CHEMICAL WORKS, INC.

Solution Digilanid: 2 and 4 cc ampuls. A solution in alcohol, glycerin and water containing 0.2 mg. of digilanid in each cubic centimeter.

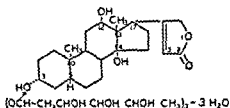
Solution Digilanid (Oral): 30 and 90 cc. vials. A solution in alcohol, glycerin and water containing 0.33 mg of digilanid in each cubic centimeter.

Suppositories Digilanid: 0.5 mg.

Tablets Digilanid: 0.33 mg.

U. S. trademark 291,301.

DIGOXIN-U.S.P.—"Digoxin is a cardiotonic glycoside obtained from the leaves of *Digitalis lanata*, Ehrh (Fam Scrophylariaceae)." U.S.P. The structural formula of digoxin may be represented as follows:



Physical Properties.—Digoxin occurs as colorless to white crystals or as a white, crystalline powder. It is colorless and melts indistinctly and with decomposition at about 235° . It is insoluble in water, in chloroform and in ether. It is freely soluble in pyridine and soluble in dilute alcohol.

to
mg at 6-hour intervals until, if auricular fibrillation is present,
the apical rate falls between 80 and 90 as the maximum there

and is maximal in 1 to 2 hours. If complete digitalization is not obtained after 6 hours, additional doses of 0.25 to 0.5 mg of digoxin may be given intravenously at 6-hour intervals.

For maintenance, 0.25 to 0.75 mg. may be given daily by mouth, or 0.25 to 0.5 mg by intravenous injection.

Digoxin injection is a tissue irritant and the contents of the ampul should be diluted with 10 cc of sterile isotonic solution. The product should be injected slowly (5 to 10 minutes) and care taken to avoid extraveneous injection.

"Caution—Digoxin is extremely poisonous." U.S.P.

BURROUGHS WELLCOME & COMPANY, INC.

Solution Digoxin, 0.05%: 1 cc ampuls. A 70 per cent alcohol solution containing 0.5 mg of digoxin in each cubic centimeter.

Tablet Digoxin, 0.25 mg.

U. S. trademark 76,731 (Tablet)

GITALIN (AMORPHOUS).—Gitaligin (Wittz)—A glycosidal constituent of *Digitalis purpurea* Linné prepared according to the method of Kraft. Dried and ground leaves are extracted with cold

water and the extract then is purified by selective precipitation and extraction technics.

Physical Properties.—Gitalin (amorphous) is a white or pale buff, amorphous powder which melts with decomposition between 110 and 150°. It is readily soluble in acetone, alcohol, chloroform and ether, slowly soluble in 600 parts of water and insoluble in carbon disulfide and petroleum ether. A saturated aqueous solution is neutral to litmus and has an intensely bitter taste.

Actions and Uses.—Gitalin (amorphous), a mixture of digitalis glycosides, has the same action and uses as digitalis itself. The rate of elimination or destruction is slower than that of digoxin but more rapid than that of digitoxin. Several investigations made in the clinic have suggested that the drug may have a more favorable ratio of therapeutic to toxic properties than other digitalis preparations, though only prolonged experience can finally determine this fact. (See the general statement on digitalis and related principles.)

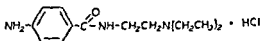
Dosage.—Gitalin (amorphous) is administered orally. For initial digitalization when rapid effects are desired, an initial dose of 2.5 mg. is followed by 0.75 mg. every 6 hours until a total of approximately 6 mg. has been given or until the full effect is manifested by toxic signs; when slower effects are adequate, a daily dose of 1.5 mg. is given for 4 to 6 days. The foregoing schedules apply only when the patient has had no digitalis or related drug for at least 2 weeks prior to the initiation of digitalization. For maintenance, the average dose is 0.5 mg. daily, preferably administered in the morning; occasionally a daily dose as low as 0.25 mg. or as high as 1.25 mg. is necessary for proper maintenance. As with all other digitalis preparations, constant supervision is essential to avoid the toxic effects of overdigitalization.

WHITE LABORATORIES, INC.

Tablets Gitaligin: 0.5 mg.

HEART MUSCLE DEPRESSANTS

PROCAINAMIDE HYDROCHLORIDE-U.S.P. — *Pronestyl Hydrochloride* (SQUIBB) — *p*-Amino-N-(2-diethylaminoethyl)benzamide hydrochloride—Procaine Amide Hydrochloride.—“Procainamide Hydrochloride contains not less than 98 per cent of $C_{13}H_{21}N_3O$ HCl, calculated on the dried basis” U.S.P. The structural formula of procainamide hydrochloride may be represented as follows:



Physical Properties.—Procainamide hydrochloride is a white to tan, odorless, crystalline solid. It melts between 165 and 169°. It is very soluble in water, soluble in alcohol, slightly soluble in chloroform and very slightly soluble in benzene and ether.

Actions and Uses.—Procainamide hydrochloride, like procaine

hydrochloride, depresses the irritability of the ventricular muscle. Unlike the latter, procainamide is hydrolyzed only slightly by plasma enzymes to *p*-aminobenzoic acid and diethylaminoethylamine so that its effect is more prolonged. Procainamide is tolerated in larger intravenous doses than is procaine; on a weight basis, the amide is about one-half to two-thirds less toxic. It differs from procaine also in that it does not produce significant central stimulatory effects. The action occurs almost immediately after intravenous administration and the plasma level declines about 10 to 13 per cent per hour; after oral administration therapeutic levels are attained within 30 minutes to one hour. Plasma levels and urinary excretion rates following oral administration are comparable to those following intravenous injection, indicating almost complete absorption of the drug by the gastro-intestinal tract. About 60 per cent is excreted unchanged, some probably is hydrolyzed as indicated above, the fate of the remainder is unknown.

Procainamide hydrochloride is useful for the treatment of ventricular and auricular arrhythmias and extrasystoles occurring either in cardiac diseases or during general anesthesia. When administered intravenously the drug produces a hypotensive effect that is less severe than that with procaine, this effect is partially due to vasodilatation. Hypotensive reactions may be precipitous and clinical judgment is required to determine whether it is necessary to administer vasoconstrictor agents or to discontinue therapy. Epinephrine is likely to aggravate an existing arrhythmia and is generally contraindicated, therefore, during cyclopropane anesthesia. Until more conclusive evidence becomes available procainamide hydrochloride is not recommended for the prevention of cardiac arrhythmias, anticipated in either conscious or unconscious subjects.

Leukopenia and granulocytopenia have followed the repeated use of the drug, so that it is imperative to obtain a blood count at regular intervals and to instruct patients to report promptly symptoms indicating the possible development of agranulocytosis. The drug should be discontinued promptly when such symptoms are accompanied by a significant reduction in the white blood cell count.

Dosage.—In conscious patients for the treatment of ventricular tachycardia, 1 Gm is given orally, followed by 0.5 to 1 Gm every 4 to 6 hours as indicated, or 0.2 to 1 Gm (2 to 10 cc of a solution containing 100 mg in each cubic centimeter) administered intravenously at a rate not greater than 1 cc per minute. For the treatment of auricular arrhythmias, the total daily oral dose ranges from 1 to 5 Gm given in three or four divided doses. Initially 1.25 Gm may be given, followed by 0.75 Gm if there are no electrocardiographic changes. Several further doses of 0.5 to 1 Gm may then be given every 2 hours until the auricular arrhythmia is eliminated. A maintenance dose of 0.5 to 1 Gm every 3 to 6 hours is suggested. The intravenous dose averages 0.5 Gm, although up to 1 Gm sometimes is given. For the treatment of runs of ventricular extrasystoles, 0.5 Gm is given orally every 4 to 6 hours as indicated. During anesthesia, 0.1 to 0.5 Gm is admin-

istered intravenously at a rate not greater than 0.2 Gm. (2 cc.) per minute.

Occasional transient electrocardiographic changes resembling those of quinidine intoxication have been observed with procainamide hydrochloride. Intravenous injection is subject to the danger of hypotensive action; oral administration is not.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Capsules Pronestyl Hydrochloride: 0.25 Gm.

Solution Pronestyl Hydrochloride: 10 cc. vials. A solution containing 100 mg. of procainamide hydrochloride in each cubic centimeter. Preserved with 0.9 per cent benzyl alcohol and 0.09 per cent sodium bisulfite

U. S. trademark 557,523.

HYPOTENSIVE AGENTS

In this group of agents are included those preparations used primarily for the treatment of essential hypertension. Sympatholytic and adrenolytic agents useful in the treatment of vasospastic conditions and the diagnosis of pheochromocytoma are discussed in the chapter on autonomic drugs

ALKAVERVIR.—*Veriloid* (RIKER).—Alkavervir is a mixture of alkaloids obtained by the selective extraction of *Veratrum viride*-N.F. with various organic solvents and selective precipitation from acidic and basic solutions.

Physical Properties.—Alkavervir is a light yellow powder with a strongly sternutatory action. It is freely soluble in alcohol and acetone, but is practically insoluble in water.

Actions and Uses.—Alkavervir is a reproducible extract of *Veratrum viride* assayed for the total hypotensive effect of its component alkaloids. When administered intravenously, it produces prompt lowering of the blood pressure and concomitant slowing of the heart rate in both normotensive and hypertensive animals and man. The mechanism of action is believed to be a centrally induced dilatation of arterioles accompanied by constriction of the venous vascular beds. Its action on smooth muscle of the gastrointestinal tract is spasmogenic. Cardiac output and cerebral blood flow are not reduced, nor is renal function compromised. Its hypotensive effect reduces both systolic and diastolic tension independent of alterations in heart rate. The extract produces variable effects on the blood flow, but has not increased the number or severity of attacks in patients with angina. The chief side effects in order of appearance are substernal or epigastric burning, sali-

respiratory depression which may progress at toxic levels to bronchiolar constriction and apnea. Cardiac arrhythmias may occur rarely and can be controlled by atropine. No drug has been found that will overcome the side effect of nausea. The extract is absorbed readily by the gastro-intestinal and usual parenteral routes. The extract apparently undergoes slow destruction by mobilization from its receptors, presumably in the brain. Tachyphylaxis and tolerance to its hypotensive action have not been observed clinically.

Alkavervir is effective when given orally or parenterally. The oral route is indicated in mild, moderate and malignant hypertension when blood pressure may be lowered gradually and when the potential benefit, in terms of decreased symptoms and increased life expectancy, outweighs the potential discomfort during the period of dose adjustment. The parenteral route is used when blood pressure must be lowered rapidly, as in the treatment of hypertensive crises for selected cases of eclampsia, pre-eclampsia, toxemia of pregnancy, acute glomerulonephritis and hypertensive encephalopathy. It should be employed with care in chronic uremia because such patients may have difficulty in adjusting to lowered blood pressure levels. It should be used with caution in patients receiving quinidine therapy. It is contraindicated in hypotension, coarctation of the aorta, pheochromocytoma (less effective than other measures), digitalis intoxication and high intracranial pressure not secondary to hypertension. Anesthetic agents do not interfere with hypotensive action of the extract, but their effect on blood pressure must be considered in determining the dose of alkavervir when it is used in conjunction with anesthesia. Drugs of the morphine series have additive but not synergistic action with the bradycardiac action of alkavervir. It also summates the heightened cardiac irritability produced by digitalis. It is considered unwise to employ diuretics during hypotensive therapy.

Dosage.—Alkavervir is administered orally and parenterally. Intravenous injection provides a more prompt hypotensive effect than does intramuscular injection. Oral administration produces less intense and still slower action, hypotensive effect is reached after 2 hours but is more lasting—4 to 6 hours.

Alkavervir is administered intravenously as a dilution of the solution containing 0.4 mg. of the dried extract per cubic centimeter. The dosage for the initial injection is estimated on the basis of 0.15 cc. of such solution for each 4.53 Kg. (10 lb.) of usual or estimated body weight, whichever may be lower. This amount then is diluted to 10 cc. with sterile isotonic sodium chloride solution or 5 per cent dextrose solution. The speed of injection should be at the rate of 0.5 cc. of the diluted solution per minute for a total of 4 cc. (8 minutes), and a check of the blood pressure should be made at least once every minute. After a wait of 2 minutes, the injection is continued at the same rate, again checking blood pressure until an additional 3 cc. (6 minutes) are given. Following another interval of 2 minutes, the injection is resumed at the same rate and the blood pressure is observed closely until the remaining 3 cc. of diluted solution is injected.

The administration should be interrupted whenever either the systolic or diastolic blood pressure falls as much as 20 mm. of mercury and it should be discontinued if either gross irregularity of the pulse or emesis occurs, particularly if neither symptom was present before the injection was started.

An interval of 2 minutes should be allowed following the initial injection to permit stabilization of blood pressure and to determine if an additional injection is necessary.

If a fall in tension does not result from the first 10 cc. of diluted solution, after 5 minutes the syringe is refilled with the same dilution and the same procedure is followed for the first 20 minutes. Some patients may require a total of 15 cc. or more of diluted solution before the desired level of blood pressure is obtained. The effect of the amount required to reduce pressure to the desired level usually persists for 30 to 45 minutes and requires an interval of $1\frac{1}{2}$ to 3 hours to return to the hypertensive level.

In encephalopathic patients, after the blood pressure has been reduced by the initial injection, two methods of maintaining pressure at the desired level may be followed according to the judgment of the clinician. Maintenance therapy can be provided by almost continuous slow intravenous infusion to keep the tension at the desired level for as long as this is feasible, usually several days, or by repeated slow injections like those used initially. With the latter method, the blood pressure is allowed to return to the preceding preinjection level between each injection until reflex adjustment takes place and previous hypertensive levels no longer occur. As many as six such injections have been employed in a single case. For the first method of maintenance, the dosage is based upon 0.6 cc. of undiluted solution per 4.53 Kg. (10 lb.) of body weight. This solution is added to a liter of 5 per cent dextrose solution for injection and administered at the rate of 30 drops per minute. The usual effective dose by this method does not exceed 100 cc. of the diluted solution per hour. The infusion should be maintained at a rate that will hold blood pressure to the desired level without inducing emesis.

It is important that a period of rapid infusion should not occur during the time when the rates of flow are being adjusted. During infusion the patient should be under constant observation and the blood pressure checked at least every 10 to 15 minutes. A solution of ephedrine sulfate 2.5 per cent (25 mg.) to combat an excessive fall in blood pressure and of atropine sulfate 1:1,000 (1 cc. ampul) to overcome bradycardia should be available at the bedside for intramuscular injection whenever this may become necessary during the administration of alkavervir.

Alkavervir is administered intramuscularly as a solution containing 1 mg. of the dried extract per cubic centimeter. When this route is used to prolong the hypotensive action following intravenous therapy, the intramuscular dose can be translated from the body weight of the patient and the previous dose in cubic centimeters of the diluted intravenous solution of 0.4 mg. per cubic

centimeter. Thus, if the previous diluted intravenous dose was 5 or 6 cc, a patient weighing 63.5 to 74.8 Kg (140 to 165 lb) would require a dose of 0.5 cc. of the intramuscular concentration for conversion of the diluted intravenous dose to the intramuscular dose.

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the blood pressure should be determined during the first hour at not less than 15 minute intervals. A tourniquet may be useful to slow absorption if there are early signs of overdose. The intramuscular dose produces its maximum effect in about 60 to 90 minutes. Subsequent intramuscular doses should be administered when the blood pressure has returned to about three-fourths of the original pretreatment level. When the first dose is too small to lower the pressure, a further injection should not be administered until a lapse of 2 to 3 hours following the initial dose. The size of the second and subsequent intramuscular doses should be governed by the response of the patient to the previous injection. For adults the dose should be adjusted by 0.25 cc increments or decrements, using proportionately smaller deviations in children. Alkavervir is administered orally in a daily dosage of 9 to 13 mg, given in three divided doses every 6 to 8 hours. The first dose should be administered after breakfast, the evening dose may be 1 or 2 mg larger than the other two doses of the day. Starting dosage should be smaller for patients of light weight with mild to moderate hypertension, larger starting doses may be used for overweight persons or persons with severe hypertension. Dosage must be individualized to the maximum that can be tolerated without nausea or other manifestation of excessive intake. Increases should never exceed more than 1 mg per dose (three times daily) nor be made oftener than every 3 to 4 days. Mild reactions (esophageal and/or substernal burning with or without diarrhea) are valuable indicators of dosage limits and should be followed by reduction in dosage. Periodic interruptions in therapy may be necessary to prevent the tendency toward nausea. Occasionally, tolerated doses may relieve symptoms without producing a significant drop in blood pressure.

RIKER LABORATORIES, INC.

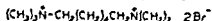
Solution Veriloid (Intravenous) 5 cc ampuls A 0.25 per cent acetic acid solution containing 0.4 mg of alkavervir in each cubic centimeter

Solution Veriloid with Procaine Hydrochloride 1% (Intramuscular) 2 cc ampuls A 0.25 per cent acetic acid solution containing 1 mg of alkavervir in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol and 0.1 per cent sodium bisulfite

Tablets Veriloid 1, 2 and 3 mg
U S trademark 352,996

HEXAMETHONIUM BROMIDE.—Bistrium Bromide (Squibb).—

Hexamethylenebis(trimethylammonium bromide).—The structural formula of hexamethonium bromide may be represented as follows:



Physical Properties.—Hexamethonium bromide is a white, tasteless, crystalline material with a faintly aromatic odor. Hexamethonium bromide is freely soluble in methanol and water, soluble in alcohol and insoluble in ether. The pH of a 1 per cent solution is 6.2 to 7.0.

Actions and Uses.—Hexamethonium bromide is similar in its actions and uses to the salts of other quaternary ammonium compounds, such as tetraethylammonium chloride, which act as ganglionic blocking agents. Hexamethonium inhibits the transmission of nerve impulses through both the sympathetic and parasympathetic ganglia of the autonomic nervous system. Interference with the transmission of sympathetic stimuli causing vasospasm, particularly in the lower extremities, produces increased blood flow and hypotension. Simultaneous interference with the transmission of parasympathetic impulses produces loss of ocular accommodation, cessation or decrease of motility of the gastro-intestinal tract and alteration of bladder function.

Hexamethonium bromide is of limited clinical usefulness as a therapeutic and diagnostic agent in the management of peripheral

selected cases of hypertension. The drug is more effective for controlling episodes of severely elevated blood pressure than for mild

ischemia, cerebral ischemia or encephalopathy and renal insufficiency.

Since hexamethonium is absorbed more slowly and less completely by oral administration than by parenteral injection, the oral route is not recommended in the therapy or diagnosis of peripheral vascular disease. Because larger doses are required to produce the effects of the drug by the oral route, the use of the bromide salt in hypertension involves the regular occurrence of bromidism, so that it should be administered only by parenteral injection. Injections of the drug are not cumulative, but tolerance

Hexamethonium may produce peripheral circulatory collapse. Because of its hypotensive action, it should be employed with caution in all elderly patients and in those with arteriosclerosis. Its use is dangerous in patients who have recently lost blood because compensatory vasoconstrictor mechanisms are blocked. Side effects occasionally observed include dilatation of the pupils, blurred vision, dryness of the mouth, postural faintness, transient nausea, vomiting or drowsiness. Constipation may occur in some patients, which often can be managed by the concomitant administration of laxatives, repeated enemas or temporary discontinuance of the drug. When the constipation is serious, paralytic ileus may result. This may be overcome by the oral administration of bethanecol chloride in doses of 5 to 10 mg twice daily. Phenylephrine hydrochloride, 2 to 4 mg intravenously, may be used to combat profound hypotension. Small doses should be used because hexamethonium increases the sensitivity to vasopressor agents.

Dosage.—Hexamethonium bromide is administered by parenteral injection, intravenously, intramuscularly or subcutaneously, depending on the rapidity of response desired. To induce ganglionic block, 90 to 135 mg (50 to 75 mg in terms of the ion) is given parenterally as a single dose. Heavier patients may require as much as 180 mg (100 mg as the ion), but the maximum dose seldom should exceed 90 mg. This produces a maximum response within a few minutes, which lasts for 1 hour and subsides gradually after 4 to 6 hours.

When repeated doses are necessary, the minimum effective dose is repeated every 6 hours, after meals and at midnight. Doses of 90 mg or more may cause profound postural hypotension and occasionally a significant reduction in supine blood pressure. Patients receiving such doses for the first time should be kept in a recumbent position for 3 hours following the initial dose. Upon arising, each patient should be instructed to lie down at the first feeling of faintness. Subsequent doses usually do not cause such profound hypotension because of vascular adjustments. The initial dose may be given subcutaneously with the patient in a sitting position as an added precaution. For severely ill or debilitated patients, an initial dose of 1.8 to 9 mg (1 to 5 mg as the ion) should be used. This should be increased gradually, depending upon the response of the patient.

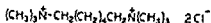
E. R. SQUIBB & SONS, DIVISION OF OLIN MATTHEWSON CHEMICAL CORPORATION

Solution Bistrium Bromide. 10 cc vials. A solution containing 44.75 mg of hexamethonium bromide in each cubic centimeter. Preserved with 0.9 per cent benzyl alcohol.

U. S. trademark 562,557

HEXAMETHONIUM CHLORIDE.—Bistrium Chloride (SQUIBB)—Esomid Chloride (CIBA)—Hexameton Chloride (BETHOUZES WELLCOME)—Hioher Chloride (HEMSELIN)—Methium Chloride (WARNER-CHILCOTT)—Hexamethylenebis(trimethylammonium chloride)—Hexamethonium chloride is available commercially in

an anhydrous form and as a dihydrate. The moisture content of the dihydrate is no more than 13.3 per cent. The structural formula of hexamethonium chloride may be represented as follows:



Physical Properties.—Hexamethonium chloride is a white, crystalline, hygroscopic powder with a faint odor. It has a melting point between 289 and 292° (with decomposition). It is very soluble in water, soluble in alcohol, methanol and n-propanol and insoluble in chloroform and ether. The pH of a 10 per cent solution is between 5.5 and 6.5.

Actions and Uses.—See the monograph on hexamethonium bromide.

Dosage.—Hexamethonium chloride, on the basis of comparative molecular weights, provides about seven-eighths and one-third more of the cation than the same doses of the bitartrate and bromide salts, respectively. The magnitude of this difference is significant only in the comparative dose of the bitartrate, particularly when the drug is administered parenterally.

Orally, for hypotensive effect, the average total daily dosage should not exceed 3 Gm., as much as 4 to 5 Gm. may be tolerated by some patients. For moderate to severe essential hypertension or malignant hypertension, the recommended initial dose is 0.125 Gm. four times daily (total of 0.5 Gm. each day), for patients on salt-free diets or patients who have been subjected to sympathectomy, the initial dose is 0.125 Gm. one or two times daily. These dosages may be increased gradually to tolerance. Adequate ganglionic blockade is determined by the presence of the unavoidable side effects. When this does not lower the blood pressure to the desired level, further increases in dosage are unwarranted. Use of the drug may be continued if it relieves symptoms without further effect on the blood pressure. Reduction in the dosage to eliminate side effects results in ineffectual ganglionic blockade.

Parenterally, for peripheral vascular disease or for hypotensive effect, a solution of hexamethonium chloride may be injected in single doses of 50 to 100 mg. of the salt, and repeated every 6 hours as necessary. The maximum dose seldom should exceed 65 mg., but heavy patients may require doses up to 135 mg. For severely ill or debilitated patients, an initial trial dose of 1.3 to 6.5 mg. should be used. This may be increased gradually to tolerance.

BURROUGHS WELLCOME & COMPANY, INC.

Solution Hexameton Chloride: 10 cc. vials. A solution containing 33.8 or 135 mg. of hexamethonium chloride (25 or 100 mg. of hexamethonium ion, respectively) in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

Tablets Hexameton Chloride: 0.25 and 0.5 Gm.

U. S. trademark 572,762

CHEMO PURO MANUFACTURING CORPORATION

Powder Hexamethonium Chloride: Bulk; for manufacturing use.

CIBA PHARMACEUTICAL PRODUCTS, INC.

Syrup Esomid Chloride: 473 cc. bottles. A syrup containing 62.5 mg of hexamethonium chloride in each cubic centimeter. Preserved with 0.1 per cent sodium benzoate.

Tablets Esomid Chloride: 0.25 Gm.

VICTOR M. HERMELIN & COMPANY, NEW PRODUCTS DIVISION OF
KEITH-VICTOR PHARMACAL COMPANY

Tablets Hiohex Chloride: 0.125 and 0.25 Gm

HEXAGON LABORATORIES, INC

Powder Hexamethonium Chloride: Bulk; for manufacturing use.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL
CORPORATION

Solution Bistrium Chloride. 10 cc vials. A solution containing 0.135 Gm of hexamethonium chloride (0.1 Gm of hexamethonium ion) in each cubic centimeter. Preserved with 0.9 per cent benzyl alcohol.

U. S. trademark 562,557.

WARNER-CHILCOTT LABORATORIES, DIVISION OF WARNER-HUDNUT,
INC.

Tablets Methium Chloride: 0.125, 0.25 and 0.5 Gm.

U. S. trademark 563,616

PROTOVERATRINES A AND B—*Veralba* (PITMAN-MOORE).—Protoveratrine A and B is a mixture of two alkaloids, isolated by appropriate means from *Veraltrum album*. The structural formula of the two alkaloids is not known.

Physical Properties.—Protoveratrine A and B is a white, odorless, slightly bitter, crystalline powder with a strongly sternutatory action, which melts between 256 and 262° (with decomposition). It is freely soluble in chloroform, very slightly soluble in ether and practically insoluble in petroleum ether and in water. Protoveratrine A and B is stable to light and air. It is stable for several months in solutions of pH 4.0 to 6.0 but is destroyed rapidly in basic and alcoholic solutions. The pH of a saturated solution is 6.3 to 7.3.

Actions and Uses.—Protoveratrine A and B exert their primary effect on the cardiovascular system by their influence on buffer-reflex receptors; with therapeutic doses the mixture induces vasodilation through effects at those sites. Some investigators believe that this results in a normal physiologic redistribution of blood to all vascular beds, resulting in postural hypotension that is less severe and less frequent than with ganglionic blocking agents. Comparison of the two components of protoveratrine used in experimental animals reveals no qualitative differences in action,

but protoveratrine B has about 80 per cent of the potency of protoveratrine A.

Protoveratrines A and B may be useful in the symptomatic treatment of essential hypertension, as in chronic renal hyper-

is much more certain following intravenous or intramuscular injection than after oral administration. As with other Veratrum alkaloids, the response of different patients varies considerably and, by the oral route, the response of an individual patient occasionally varies.

In some patients. When pronounced impairment of renal function exists, adequate control of the hypertension is unlikely. Because of their hypotensive action, protoveratrines A and B may alleviate such symptoms as headache, insomnia, delirium, dizziness, blurred vision and nervousness. Their slowing effect on the heart rate may be followed by a reduction in the degree of congestive heart failure when this is caused by left ventricular failure associated with hypertension. Protoveratrines A and B also reduce hypertensive pulmonary edema and lower the elevated blood pressure occasionally encountered with cortisone therapy, they may be useful also in controlling convulsions of eclampsia.

Like other Veratrum alkaloids, overdosage of protoveratrines A and B produces disturbing, toxic side effects, and with therapeutic

tightness is experienced. Unless bradycardia is severe and associated with arrhythmias, it is not necessarily harmful and may be desirable in cases of tachycardia with circulatory failure. Severe bradycardia may be overcome by an intravenous or intramuscular injection of 0.4 mg of atropine sulfate. Parenteral injection, especially when administered too rapidly by the intravenous route, may produce sudden, excessive hypotension accompanied by collapse. This can be treated best by intramuscular injection of vasopressor drugs, such as ephedrine (25 mg) or phenylephrine (5 mg.). A feeling of warmth over the epigastrium, perineum, face or extremities is commonly observed, but this reaction is of minor importance and usually not unpleasant; however, gross irregularity of the pulse and nausea or vomiting appearing during intravenous administration indicate the beginning of overdosage and the need to discontinue injection. These signs (particularly nausea which is not previously present) serve as a guide to the tolerated dosage.

Protoveratrine A and B should be employed cautiously in chronic uremia because such patients may have difficulty in adjusting to lowered blood pressure levels. Caution also is necessary in the presence of digitalis intoxication. Protoveratrine A and B are contraindicated in hypotension and high intracranial pressure not

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mum dosage schedule. Usually, this can be done best if the patient is hospitalized. The stabilized resting diastolic and systolic blood pressures should be determined prior to initiating therapy.

For the management of moderate hypertension, the usual starting oral dose for adults is 0.5 mg. after each meal and at bedtime. The blood pressure should be determined 2 to 3 hours following

lowered significantly, each of the four doses may be increased 0.2 mg. for the next day. Subsequent daily doses may be increased similarly until a satisfactory response is obtained. If nausea, vomiting or other side effects appear before an effective dosage level is established, the dose should be reduced by 0.1 or 0.2 mg., as may be necessary to obtain the desired effect just short of the signs of overdosage. The average effective dose varies from 0.4 to 1.5 mg. four times daily. Shorter or longer intervals may be used; or differential doses, such as a larger morning or bedtime dose with smaller interim doses, may be more effective in some patients.

Parenteral injection for the management of hypertensive crises should be initiated by the intravenous route according to one of the following methods: (1) An initial dose of 0.06 to 0.1 mg. (0.3 to 0.5 cc.) is administered slowly. If no significant decrease in blood pressure occurs, an increment of 0.02 mg. (0.1 cc.) can be repeated in 4 hours, and, if necessary, the dose can be increased by the same increment at 4-hour intervals until the desired response is obtained. As the optimal response is approached, increments of 0.01 mg. (0.05 cc.) are preferable. When toxic signs occur, one or two doses can be omitted and therapy recommenced at a lower dose. If a particularly prompt effect is necessary, the initial dose may be followed by small doses of 0.02 mg. (0.1 cc.) at 15-minute intervals. Maximum response usually appears 10 to 30 minutes after intravenous injection. Duration of action of a single intravenous dose extends about 1½ to 3 hours, but cumulative effects can result even when injections are spaced at longer intervals. (2) Slow intravenous infusion can be employed by using a more dilute solution prepared by dissolving 2 mg. of protoveratrine A and B in 200 cc. of either isotonic sodium chloride solution or 5 per cent dextrose to make a concentration of 0.001 mg. per cubic centimeter. Infusion of this dilution at the rate of 3 to 6 cc. every 10 minutes usually will decrease blood pressure significantly, and 1 to 3 cc. administered each 10 minutes is the approximate main-

tenance rate. (3) An alternate method of interrupted injection is the use of a 10 cc. syringe dilution of 0.1 mg. in either isotonic sodium chloride solution or 5 per cent dextrose to make a concentration of 0.01 mg. per cubic centimeter. This dilution is given at the rate of 0.5 cc. per minute for 8 minutes (total 4 cc.), during which time the blood pressure is observed continuously. After an interval of 2 minutes, the same rate is continued for 6 more minutes (3 cc.; total 7 cc.). After another 2-minute interval, the injection is continued at the same rate for an additional 6 minutes, during which time the blood pressure is checked closely (total 10 cc., which exhausts the supply in the syringe). The injection should be interrupted whenever either the systolic or diastolic pressure falls 20 mm. Hg. Three minutes is allowed for stabilization of blood pressure at the new level. If no fall results from the first 10 cc., 5 minutes should elapse; then the syringe is refilled with the same dilution, and the previous procedure is repeated. The amount required may range from 5 to 20 cc. or more, but the

syringe method instead of continuous infusion to maintain the effect of the initial injection, repeating that procedure after the blood pressure has returned to a hypertensive level.

Intramuscular injection also can be used to maintain the initial response to intravenous therapy. The mixture is administered in doses of 0.16 to 0.4 mg. (0.8 to 2 cc.) every 4 to 8 hours. An alternative method is to inject an initial dose of 0.12 mg. (0.6 cc.), taking the blood pressure every 15 minutes thereafter. The maximum effect usually appears within 1 to 2 hours. If the desired response does not occur, a dose of 0.16 mg. (0.8 cc.) can be repeated after an interval of not less than 4 hours. This can be followed with 0.2 cc. increments not oftener than every 4 hours until the desired lowering of the blood pressure results. The dose established by this method usually can be repeated if the interval between injections is not less than 4 hours. Six-hour or 8-hour intervals also may be effective.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

Solution Veralba: 10 cc. vials. A solution containing 0.2 mg. of protoveratrine A and B in each cubic centimeter. Preserved with 0.2 per cent *m*-cresol.

Tablets Veralba: 0.2 and 0.5 mg.

PROTOVERATRINE A AND B MALEATES.—Provell Maleate (LILLY).—The maleate salt of a mixture of two alkaloids, isolated by appropriate means from *Veratrum album*.

Physical Properties.—Protoveratrine A and B maleates is a white

to buff colored powder with a faint characteristic odor and a strong sternutatory action, with a melting point between 210 and 220° C.

same actions and uses as the parent esters, protoveratrine A and B. See the monograph on protoveratrine A and B. The same precautions should be observed in the use of the maleate as with the parent form of the mixture.

Dosage.—Protoveratrine A and B maleates are administered orally. On the basis of comparative molecular weights, approximately 13 per cent more of the maleate salts than of the parent esters is required to provide equivalent dosage; however, the difference is not of particular significance except when therapy may be alternated in patients for whom optimal maintenance dosage has been individualized. Careful adjustment of the dosage for each patient is essential.

The average oral total daily dosage ranges from 1 to 25 mg, divided into three to five doses, preferably given after meals and

later in the day.

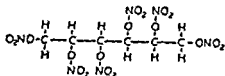
ELI LILLY & COMPANY

Tablets Provel Maleate: 0.5 mg.

Organic Nitrates

The esters of nitric acid and the higher alcohols (such as glycerin, propanetriol, erythrite and butsnetetrol) have an action on the blood vessels similar to that of the inorganic nitrites (sodium nitrite) and that of the nitrous acid esters of the alcohols (amyl nitrite, ethyl nitrite). Generally, this is attributed to the fact that they form nitrites in the body.

MANNITOL HEXANITRATE.—An explosive compound formed by the nitration of mannitol, a sugar alcohol. The stability of the pure compound at ordinary temperatures is such that it may be used commercially, but it is distinctly less stable than nitroglycerin at 75°. It is marketed only in admixture with carbohydrate substances in dilutions of 1 part of mannitol hexanitrate to 9 or more parts of carbohydrate. In such dilutions mannitol hexanitrate is nonexplosive. The structural formula of mannitol hexanitrate may be represented as follows:



Physical Properties.—Mannitol hexanitrate is partially soluble in alcohol, ether and water (lactose).

Actions and Uses.—Mannitol hexanitrate exerts the same action of the nitrite ion (NO_2^-) as sodium nitrite.

It also relaxes the coronary vessels in experimental animals. The action is too slow to give effective relief to attacks of angina pectoris, and, when given regularly throughout the day, it has not been proved useful in preventing attacks. The drug does not benefit most cases of essential hypertension, as it does not permanently lower blood pressure. It has no direct effect on the myocardium.

Toxic effects include the formation of methemoglobin (a warning against the use of nitrites in anemic persons), rise in intraocular tension, headache, increase in intracranial pressure and cardiovascular collapse.

Dosage.—Mannitol hexanitrate may be administered in 15 to 60 mg. doses at intervals of 4 to 6 hours.

THE BOWMAN BROS. DRUG COMPANY

Tablets Mannitol Hexanitrate: 32 mg.

COLE CHEMICAL COMPANY

Tablets Mannitol Hexanitrate: 32 mg.

DIRECT LABORATORIES, INC.

Tablets Mannitol Hexanitrate: 16 and 32 mg.

KEITH-VICTOR PHARMACAL COMPANY

Tablets Mannitol Hexanitrate: 30 mg.

THE NATIONAL DRUG COMPANY

Tablets Mannitol Hexanitrate: 30 mg.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Mannitol Hexanitrate: 30 mg.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Mannitol Hexanitrate: 32 mg.

RAYMER PHARMACAL COMPANY

Tablets Mannitol Hexanitrate: 32 mg.

WILLIAM H. RORER, INC.

Tablets Mannitol Hexanitrate: 32 mg.

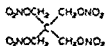
E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIASSEN CHEMICAL CORPORATION

Tablets Mannitol Hexanitrate: 16 and 32.5 mg.

S. J. TUTAG & COMPANY

Tablets Mannitol Hexanitrate: 32.4 mg.

PENTAERYTHRITOL TETRANITRATE.—Peritrate Tetranitrate (WARNER-CHILCOTT).—Pentaerythritol tetranitrate for medicinal purposes is diluted with an inert ingredient, such as lactose, since the undiluted compound may explode upon percussion. The structural formula of pentaerythritol tetranitrate may be represented as follows:



Physical Properties.—Pentaerythritol tetranitrate is a white crystalline powder. It is soluble in acetone, slightly soluble in alcohol and insoluble in water.

Actions and Uses.—Pentaerythritol tetranitrate has the same properties as other slow-acting vasodilator organic nitrate compounds, the action of which is ascribed to the release of the nitrite ion in the body. Chemically it bears a closer structural resemblance to glyceryl trinitrate (nitroglycerin) than to either erythryl tetranitrate or mannitol hexanitrate. Pentaerythritol tetranitrate releases smaller amounts of nitrite for longer periods. The drug is not intended to replace the use of glyceryl trinitrate for immediate relief of anginal attacks. Present evidence does not indicate that the drug possesses significant value in the management of hypertension. Little effect is produced on the heart rate. Moderate increase occurs in the rate and volume of respiration.

Tolerance does not appear to develop to pentaerythritol tetranitrate and significant toxic manifestations have not been observed in the patients so far studied. Side effects are the same as those of other nitrates, except that these appear to be relatively infrequent and methemoglobinemia has not been demonstrated following prolonged use. Transient headache and nausea, occasionally observed, tend to disappear after 4 or 5 days of medication and have not

been sufficiently severe to require discontinuing treatment. Like all nitrates, the drug should be given with caution in glaucoma, but anemia so far is not considered to be a contraindication to its use.

Dosage.—Pentaerythritol tetranitrate is administered orally in doses of 10 to 20 mg. three to four times daily, as may be required for maximal effect. For certain patients, adherence to a regular dosage schedule of not less than 10 mg. three or four times daily may reduce the number of anginal attacks or the severity of those attacks which are not prevented.

CHEMO PURO MANUFACTURING CORPORATION

Powder Pentaerythritol Tetranitrate: Bulk; for manufacturing use
A mixture containing 75 mg. of pentaerythritol tetranitrate in each gram of powder.

WARNER-CHILCOIT LABORATORIES, DIVISION OF WARNER-HUDNUT, INC.

Powder Peritrate Tetranitrate: 30 Gm. bottles. A mixture containing 45.5 mg. of pentaerythritol tetranitrate in each gram of powder.

Tablets Peritrate Tetranitrate: 10 mg. plain and enteric coated; 20 mg. plain.

U. S. trademark 558,709.

Central Nervous System Depressants and Stimulants

This chapter includes agents that act principally as depressants of the central nervous system which may be used to induce sleep if pain is absent or to control convulsions. This group is to be distinguished on the one hand from the analgesics which are used to relieve pain, and on the other hand from the antispasmodics which primarily depress muscular activity. Some sedative compounds, notably the barbiturates, may be administered in doses sufficient to produce general anesthesia. Morphine and its derivatives, used mainly as analgesics, are included along with opium principles in the chapter on analgesics.

This chapter also describes drugs that stimulate the central nervous system. Picrotoxin has been included because it is particularly valuable in combating the depression of severe barbiturate intoxication.

Certain autonomic drugs that produce conspicuous central stimulating effects are considered. Aminophylline, which is useful in combating Cheyne-Stokes respiration because of its central stimulating action, is described with other theophylline and theobromine preparations in the chapter on diuretics.

CENTRAL NERVOUS SYSTEM DEPRESSANTS

Barbituric Acid Derivatives

Chemistry.—Barbituric acid is a cyclic compound obtained by the combination of urea and malonic acid; it is also called malonyl urea. It may exist as a "keto" form (1), or as an "enol" form (2):



1



2

The latter is acidic in nature, the hydrogen atom at position 2

tures have aliphatic radicals substituting for the hydrogen atoms; a few have alicyclic radicals. Phenobarbital is the only important barbiturate that contains an aromatic radical. Other variations in structure include the substitution of halogen for one of the hydrogens attached to the carbon in position 5, the substitution of an organic radical for the hydrogen attached to either of the nitrogens, and the replacement of oxygen attached to the carbon in position 2 with sulfur to form a thiobarbiturate.

The following compounds and their salts are official, are included in this chapter or have been described in previous editions of *New and Nonofficial Remedies*:

DURATION OF ACTION	COMPOUNDS	R ¹	SUBSTITUENTS R ²	Other
Long	Darbital	Ethyl	Ethyl	
Long	Mephobarbital	Ethyl	Phenyl	1-Methyl
Long	Phenobarbital	Ethyl	Phenyl	
Intermediate	Amobarbital	Ethyl	Isoamyl	
Intermediate	Apobarbital	Allyl	Isopropyl	
Intermediate	Butobarbital	Ethyl	1-Methylpropyl	
Intermediate	Sodium Diallylbarbituric Acid	Allyl	Allyl	
Intermediate	Probarbital Calcium and Sodium	Ethyl	Isopropyl	
Intermediate	Vinbarbital Sodium	Ethyl	1-Methyl-1-butenyl	
Short	Cyclobarbital	Ethyl	Cyclohexenyl	
Short	Hexethal Sodium	Ethyl	n-Hexyl	
Short	Pentobarbital	Ethyl	1-Methylbutyl	
Short	Secobarbital	Allyl	1-Methylbutyl	
Ultrashort	Hexobarbital Sodium	Methyl	Cyclohexenyl	1-Methyl
Ultrashort	Thiamylal Sodium	Allyl	1-Methylbutyl	2-Thio
Ultrashort	Thiopental Sodium	Ethyl	1-Methylbutyl	2-Thio

Although all the barbituric acid derivatives have similar actions, they differ sufficiently so that some are effective as antiepileptics, some as hypnotics, some as anesthetics and some as sedatives. None excels in all these categories of action.

Duration of Action.—The barbiturates often are classified according to the duration of their action, as long, intermediate, short and ultrashort-acting drugs. In general, the interval between the initiation of the dose and the exhibition of its therapeutic effects is longer in the long-acting than in the intermediate-acting and ultrashort-acting compounds. The long-acting barbiturates are used to produce a prolonged mild sedation in such conditions as neurasthenia, hyperthyroid disease and to reduce the frequency of epileptic convulsions, small doses of a long-acting barbiturate are useful. The effects of the intermediate-acting barbiturates are more rapid and produce an evenly maintained sedation. The ultrashort-acting barbiturates are used to produce anesthesia by the kidney; they are also used to produce anesthesia to a large extent in the treatment of various conditions. The duration of action has been a matter of considerable interest, and it is destroyed in

the liver. The slower the excretion or destruction of the various members of this group, the more lasting is the action. With very slow excretion, prolonged administration of ordinary doses may result in cumulative toxic effects. This is especially important when the drugs are administered to patients with damaged liver or kidneys.

Uses.—The derivatives of barbituric acid are effective sedatives and hypnotics, and are used in insomnia, hysteria, neurasthenia,

sia and basal narcosis, premedication before surgical operations, the control of pain in labor, psychiatric treatment and the prevention and treatment of convulsions. The therapeutic effects are exerted on the higher centers of the brain, and therapeutic doses usually do not cause any apparent injury to the vital organs.

Simple insomnia can be divided into two categories—one in which falling asleep is difficult, but once sleep is achieved, it is undisturbed, the other in which sleep comes easily but is disturbed by nocturnal or very early morning awakening. Drugs should not be taken routinely for either type, in fact, the use of barbiturates is much abused in insomnia. However, as temporary measures they may assist in psychotherapy, or be used to promote sleep on a particularly disturbing night. For insomnia of the first type the drug of choice is a short-acting barbiturate, which produces sleep within one-half hour and whose effect disappears within 4 to 6 hours. For the second type of insomnia, the drug of choice is an intermediate-acting barbiturate, whose effect appears later and lasts 6 or 8 hours. The sleep induced by small doses of these drugs closely resembles natural sleep, and the patient generally awakens refreshed. Some persons may nap the following day. Even with the usual therapeutic doses for sleep, "hangover" the next day is common.

Barbiturates are valuable in the treatment of convulsions resulting from anesthetic drugs and most other causes. The cautious intravenous administration of a short-acting or ultrashort-acting barbiturate usually is satisfactory in stopping a severe convulsion. For prolonged control of convulsions, as in tetanus, the drugs may be given rectally.

The barbiturates are useful in controlling excitement and manic states. The intravenous barbiturates also have been found useful in the procedure of narcoanalysis. A psychiatric interview is conducted while the patient is in a semiconscious state produced by small doses of drug. Therapy of some mental disorders is rendered easier by this procedure.

The barbiturates also are used during labor, either alone or in combination with scopolamine, to produce amnesia by means of a form of twilight sleep. A frequent complication in this procedure is delirium and excitement of the mother, caused by pain which the barbiturates do not relieve. The newborn infant also is affected by

the drug given to the mother; there is an increase in the incidence of *depression* in the infant. *Respiratory depression* is a *serious complication* by *excessive dosage*.

The barbiturates commonly are used for preanesthetic medication, either alone or in combination with other drugs. A short-acting or intermediate-acting drug is administered on the evening before operation to reduce apprehension and provide a restful sleep. A short-acting barbiturate is administered, often with morphine and atropine, 1 to 2 hours before operation. The barbiturates are particularly valuable for premedication when a local or regional anesthetic is to be administered, since they reduce the frequency and severity of toxic reaction to the local anesthetic drugs. The intramuscular use of pentobarbital sodium has been found to provide the serenity and sedation desired before anesthesia more effectively than the narcotics.

Mixtures of 50 per cent nitrous oxide and oxygen may be administered advantageously to improve the anesthesia and reduce the

of venous thrombosis. Induction is rapid and pleasant.

Respiratory depression and apnea are serious complications which may occur. The anesthetist must be capable of treating these conditions and must have equipment at hand to give artificial respiration with oxygen via a laryngeal tube. Laryngospasm and vomiting may occur. Intravenous barbiturate anesthesia is especially dangerous in patients whose stomachs contain food. When this is suspected, vomiting should be induced before anesthesia is started. These drugs are contraindicated in shock and in operative procedures where shock may be expected. They also are contraindicated in patients with diminished pulmonary ventilation or respiratory obstruction, and in operations about the mouth and nose that may cause blood to run down the respiratory tract. Muscular relaxation with these drugs is poor, and attempts to increase the relaxation by the use of more barbiturates result in overdosage. Curare may be given to produce muscular relaxation during barbiturate anesthesia.

Basal narcosis may be produced by the rectal administration of short-acting or ultrashort-acting barbiturates; however, the depth of anesthesia is difficult to control. The drug is dissolved in a small volume of warm tap water and administered as a retention enema. Sleep is produced in about 10 minutes. Short minor operative procedures may be performed without further anesthesia, but for most operations the basal narcosis must be supplemented with one of the other anesthetic drugs. This method is particularly valuable for quiet induction of anesthesia in apprehensive children and in

toxic thyroid patients. Thiopental sodium may be used in this manner. Prolonged convulsive states, as in tetanus, may be controlled in this manner with reduced dosage. The precautions necessary with this method are the same as those applying in intravenous barbiturate anesthesia.

The margin between the therapeutic and toxic doses of

tients in whom they produce restlessness and excitement. All patients should be questioned as to any known sensitivity or idiosyncrasy to barbiturates before administration. Typical skin eruptions sometimes are observed, especially after prolonged administration. Long-continued use of the short-acting barbiturates may result in addiction with an abstinence syndrome which is characterized by a series of grand mal convulsions.

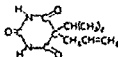
Poisoning with the barbiturates is a common occurrence, both by accident and with suicidal intent. The toxic effects of overdosage are respiratory depression, peripheral vascular collapse, feeble heart beat, lowered body temperature and long-continued stupor with depressed or absent reflexes. Death results from depression or paralysis of the respiration, or from pulmonary complications.

In the treatment of barbiturate poisoning, adequate oxygenation is of prime importance. In case of respiratory paralysis, artificial respiration should be instituted at once, either manually or by mechanical means.

The stomach should be emptied by gastric lavage with warm water. The patient should be kept warm and his position should be changed frequently in order to prevent the onset of hypostatic pneumonia. Analeptic drugs may be administered intravenously in divided doses when there is deep coma and severe respiratory depression, but recent studies indicate that analeptics given under such conditions are more dangerous than otherwise.

emerged even though the drugs may have been ingested hours before. The patient should be kept warm, and his position should be changed frequently in order to prevent the onset of hypostatic pneumonia. Analeptic drugs may be administered intravenously in divided doses when there is deep coma and severe respiratory depression, but recent studies indicate that analeptics given under such conditions are more dangerous than otherwise.

lyl-
rue-



Physical Properties.—Aprobarbital is a fine, white, odorless, crystalline powder with a slightly bitter taste. It melts between 140 and 141.5°. It is completely soluble in alcohol, chloroform and ether,

very slightly soluble in cold water and insoluble in paraffin hydrocarbons. A saturated aqueous solution is acid to litmus.

Actions and Uses.—The actions and uses of aprobarbital are essentially similar to those of barbital, but aprobarbital is more active than barbital and is used in correspondingly smaller doses. Fractional doses are used for sedation and larger doses for hypnosis.

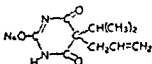
Dosage.—For mild cases of insomnia, 65 mg. may be administered at bedtime; in obstinate cases, 0.13 Gm. may be given.

HOFFMANN-LA ROCHE, INC

Elixir Aflurate: 177.4 and 473 cc and 3.78 liter bottles. A 20 per cent alcohol solution containing 8 mg. of aprobarbital in each cubic centimeter.

U. S. trademark 230,059

APROBARBITAL SODIUM.—Sodium 5-allyl-5-isopropylbarbiturate. The structural formula of aprobarbital sodium may be represented as follows:



Physical Characteristics. Aprobarbital sodium is a white, microcrystalline powder.

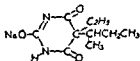
ble sodium salt is intended for particularly as preanesthesia medication. It may be used also in other cases in which a sedative is required.

Dosage.—The average preoperative dose is 10 mg. per kilogram of body weight. One-third of the calculated dose is given 10 to 12 hours prior to operation (usually the evening before), the remainder, 2 hours before operation. Experience is necessary in the use of these large dosages, as they must be adjusted to the individual patient in order to avoid undesirable reactions.

CHEMO PURO MANUFACTURING CORPORATION

Powder Aprobarbital Sodium: Bulk; for manufacturing use

BUTABARBITAL SODIUM.—Butisol Sodium (McNEIL).—Sodium 5-sec-butyl-5-ethylbarbiturate. The structural formula of butabarbital sodium may be represented as follows:



Physical Properties.—Butabarbital sodium is a white, bitter

fast-acting derivative, pentobarbital, and the long-acting barbital and phenobarbital. Following oral administration the drug usually exerts initial effects within 30 minutes. Sedation is sustained for

sodium is essentially nontoxic for the liver. Its therapeutic co-

other barbiturates.

tion of action is dependent on the size of the dose and the weight of the patient.

THE BOWMAN BROS. DRUG COMPANY

Elisir Butabarbital Sodium. 473 cc and 3.78 liter bottles. A flavored alcohol solution containing 6.6 mg of butabarbital sodium in each cubic centimeter.

Tablets Butabarbital Sodium: 16 and 32 mg.

CHEMO PICO MANUFACTURING CORPORATION

Powder Butabarbital Sodium: Bulk; for manufacturing use.

MCNEIL LABORATORIES, INC.

Capsules Butisol Sodium: 0.1 Gm.

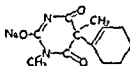
Elisir Butisol Sodium. 473 cc and 3.78 liter bottles. A flavored alcohol solution containing 6.6 mg of butabarbital sodium in each cubic centimeter.

Tablets Butisol Sodium: 15, 30, 50 and 100 mg.

U. S. trademark 378,610

HEXOBARBITAL SODIUM-N.F.—Evipal Sodium (WYETH-BRAND, STEARNS).—Sodium 5-(1-cyclohexenyl)-1,5-dimethylbarbiturate.—

"Hexobarbital Sodium yields not less than 98.5 per cent and not more than 101 per cent of $C_{12}H_{15}N_2NaO_3$, calculated on the anhydrous basis." *N.F.* The structural formula of hexobarbital may be represented as follows:



Physical Properties.—Hexobarbital sodium is a white, odorless, hygroscopic powder. It is soluble in water and in ether. A litmus. The pH of a 1% solution is between 11 and 12.

Actions and Uses.—The actions and uses of hexobarbital sodium are similar to those of pentobarbital sodium except that hexobarbital sodium is designed only for intravenous use to produce anesthesia of short duration. When injected intravenously it is a quick-acting, general anesthetic. In the majority of cases consciousness is restored in 15 to 30 minutes, depending on the amount of drug injected. Drowsiness or sleep sometimes follows if the patient is left undisturbed. While the intravenous use of barbiturates is valuable under certain circumstances it should be undertaken only by those experienced in this field. Adequate facilities should be at hand to combat untoward reactions. Ataxia and transient amnesia may be encountered occasionally. Contraindications are those of the barbital compounds and general anesthetics.

Dosage.—As there is considerable variation in individual reac-

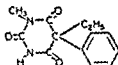
Caution.—If the solution is discolored or shows the presence of undissolved particles, it should be discarded, even if it has been freshly prepared. The powder and solution undergo change on exposure to air and should not be kept for future use.

WINTHROP-STEARNs, INC.

Powder Evipal Sodium: 1 and 5 Gm ampuls.

U. S. patent 1,947,944. U. S. trademark 315,515.

MEPHOBARBITAL-N.F.—Mebaral (WINTHROP-STEARNs).—5-Ethyl-1-methyl-5-phenylbarbituric acid. The structural formula of mephobarbital may be represented as follows.



Physical Properties.—Mephobarbital forms white, tasteless, odorless crystals which melt between 177 and 181°. It is soluble in chloroform, slightly soluble in alcohol and ether and very slightly soluble in water. Mephobarbital dissolves in fixed alkali hydroxides and carbonates.

Actions and Uses.—Mephobarbital produces the sedative effect characteristic of other members of the barbiturate series. Like phenobarbital, it is not as much affected by the development of tolerance

action in animals is not affected by the development of tolerance to other members of the barbiturate series, it is considered to have a different fate in the body than other derivatives of barbituric

when given alternately or in combination with either of those drugs. Mephobarbital is inferior to phenobarbital for the management of insane epileptics, but does control seizures in epileptic psychotic persons having only moderately advanced mental changes. It does not cure congenital mental defects or the mental deterioration often observed in epileptic persons. The drug may be used in conjunction with a ketogenic diet.

Mephobarbital also is useful as a sedative, especially in the treatment of agitated, depressed and anxiety states when minimal hypnotic action is desired. Mephobarbital produces side effects of drowsiness and gait disturbance, but these are less pronounced and less persistent than similar effects of phenobarbital. Such symp-

epilepsy, the average total daily dose for adults ranges from 0.4 to 0.6 Gm., although as little as 0.2 Gm. or as much as 0.8 Gm. may be required in some patients. Patients who have seizures principally at night and who require not more than 0.4 Gm. daily may be given the entire dose at bedtime. For attacks during the day, half the

daily dose should be given during waking hours and half at night. Children under 5 years of age may be given a total daily dose of 0.03 to 0.06 Gm. and older children 0.06 to 0.3 Gm. Treatment always should be started with a small initial dose, and doses then increased gradually over a period of 4 to 5 days until the optimum

of the latter should be reduced, but mephobarbital may be administered in the same dosage as when it is given alone. Satisfactory results have been obtained with an average daily dose of 0.225 Gm. of diphenylhydantoin sodium plus 0.6 Gm. of mephobarbital.

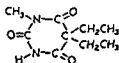
As a sedative, mephobarbital may be administered in doses of 0.03 to 0.06 Gm. three or four times daily, depending on the age and condition of the patient.

WINTHROP-STEARNs, INC.

Tablets Mebaral: 32, 50, 100 and 200 mg.

U. S. patent 1,923,239 U. S. trademark 321,093

METHARBITAL.—Gemonil (ABBOTT).—5,5-Diethyl-1-methylbarbituric acid.—The structural formula of metharbital may be represented as follows:



Physical Properties.—Metharbital is a white, crystalline powder with a faint aromatic odor. It has a melting point between 151 and 155°. The amounts that dissolve in the following solvents to form 100 cc. of solution are: 4.3 Gm. in alcohol, 2.6 Gm. in ether and 0.12 Gm. in water. The pH of a saturated solution is between 5.6 and 5.7.

Actions and Uses.—Metharbital, a derivative of barbituric acid, shares the anticonvulsant properties of phenobarbital. The drug, therefore, is useful in the treatment of various forms of epilepsy, including grand mal, petit mal and myoclonic and mixed types of seizures. It may be effective in patients whose seizures are not controlled with other anticonvulsants, particularly in the management of myoclonic seizures and in cases attributed to organic brain damage. Conversely, it may be inferior to other agents for the treatment of idiopathic forms of the disease. In experimental

relatively infrequent. Drowsiness, increased irritability, rash, dizziness or stomach distress may occur. In some patients, the drug appears to be less hypnotic and depressing than phenobarbital.

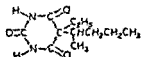
Dosage.—Metharbital is administered orally. The initial dosage for infants and small children should be 50 mg. one to three times daily; for adults, 0.1 Gm. one to three times daily. The dosage may be increased gradually depending upon tolerance; some patients may require 0.6 to 0.8 Gm. daily to control seizures.

ABBOTT LABORATORIES

Tablets Gemonil; 0.1 Gm.

U. S. trademark 541,171.

PENTOBARBITAL.—Nembutal (Abbott).—5-Ethyl-5-(1-methylbutyl)barbituric acid. The structural formula for pentobarbital may be represented as follows:



Physical Properties.—Pentobarbital is a white, granular powder. It melts between 126 and 130°. It is freely soluble in alcohol, chloroform and ether and slightly soluble in water. It dissolves in solutions of alkali hydroxides.

Acton, N. H.

calcium salts.

a dosage equivalent to
of pentobarbital is ap-
tobarbital calcium.

an elixir designed for
years, 30 mg.; 2 to 3
years, 0.12 Gm. These
before operation.

ABBOTT LABORATORIES

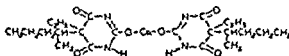
Elixir Nembutal: 473 cc. and 3.78 liter bottles. An 18 per cent alcohol solution containing the equivalent of 4 mg. of pentobarbital sodium in each cubic centimeter.

U. S. trademark 285,003.

CHEMO PURO MANUFACTURING CORPORATION

Powder Pentobarbital: Bulk, for manufacturing use.

PENTOBARBITAL CALCIUM.—Nembutal Calcium (Abbott).—Calcium 5-ethyl-5-(1-methylbutyl)barbiturate. The structural formula of pentobarbital calcium may be represented as follows:



Physical Properties.—Pentobarbital calcium is a very fine, white powder. It is sparingly soluble in alcohol and water and practically insoluble in ether.

Actions and Uses.—Pentobarbital calcium shares the actions and

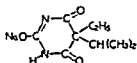
As the sodium salt, 30 mg. is administered rectally for analgesia for infants up to 1 year of age, 60 mg. for children up to 3 years of age; and 0.32 to 0.38 Gm. dissolved in a few cubic centimeters of water for adults. The average intravenous dose for adults is 0.2 to 0.3 Gm. with 0.5 Gm. as the maximum dose. The maximum dose for children has not been established definitely, although a child 6 to 12 years of age may receive up to 0.2 Gm.

ABBOTT LABORATORIES

Tablets Nembutal Calcium: 100 mg.

U. S. trademark 285,003

N.F. The structural formula of probarbital sodium may be represented as follows:



Physical Properties.—Probarbital sodium is a white hygroscopic powder, soluble in water, slightly soluble in alcohol and practically insoluble in ether and chloroform. Aqueous solutions of probarbital sodium are alkaline to litmus.

monly persists for 24 hours

Probarbital sodium is used as a hypnotic to combat restlessness, irritability and sleeplessness. Tolerance to probarbital sodium is not developed readily. It produces sleep which closely resembles the normal. The soporific effect does not wear off suddenly as with shorter-acting barbiturates

Dosage.—The sedative dose is 0.13 to 0.26 Gm.; hypnotic, 0.26 to 0.39 Gm.; preoperative, 0.52 Gm., postoperative, 0.05 Gm.

Caution.—Aqueous solutions of probarbital salts are not stable, but decompose on standing; precipitation occurs when they are boiled.

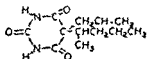
E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Elixir Ipral Sodium: 473 cc bottles. An elixir containing 13 mg. of probarbital sodium in each cubic centimeter

Tablets Ipral Sodium: 0.26 Gm.

U. S. trademark 203,813

SECOBARBITAL.—Seconal (LILLY).—5-Allyl-5-(1-methylbutyl) barbituric acid. The structural formula of secobarbital may be represented as follows



Physical Properties.—Secobarbital is a white, amorphous, odorless powder with a slightly bitter taste which melts at about 150°C. It is very soluble in water and insoluble in alcohol, ether, and chloroform. It is soluble in 8.5 cc of 0.5 N sodium hydroxide solution.

Actions, Uses and Dosage.—Same as for secobarbital sodium.

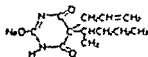
GANE'S CHEMICAL WORKS, INC

Powder Secobarbital. Bulk, for compounding use.

ELI LILLY & COMPANY

Elixir Seconal. An elixir in a vehicle containing alcohol, glycerin, methenamine, water and aromatics, containing 4.4 mg of secobarbital in each cubic centimeter. Methenamine increases the solubility of the barbituric acid.

SECOBARBITAL SODIUM (EVRON).—5-Allyl-5-(1-methylbutyl) barbituric acid sodium salt. Sodium contains not less than 98.5 per cent of $C_{12}H_{17}N_2NaO_3$, calculated on the dried basis. U.S.P. The structural formula of secobarbital sodium may be represented as follows



Physical Properties.—Secobarbital sodium is a white, hygroscopic,

odorless powder with a bitter taste. It is very soluble in water, soluble in alcohol and practically insoluble in ether. The pH of a 5 per cent solution is between 9.8 and 10.1.

Actions and Uses.—The actions and uses of secobarbital sodium are essentially those of barbital except that the former is a short-acting barbiturate. It is more active than barbital and is used in correspondingly smaller doses.

When oral administration is contraindicated, this barbiturate may be administered rectally. Small doses are sedative; larger doses are hypnotic.

Dosage.—The average adult dose is 0.1 to 0.2 Gm. For use in obstetrics and for preanesthetic sedation the following dosage has been suggested: In obstetrics, an initial dose of 0.3 Gm. followed by 0.1 to 0.2 Gm. doses at appropriate intervals up to a total of no more than 1.2 Gm. within a 12-hour period; as a preanesthetic agent, 0.2 to 0.3 Gm. one-half to one hour before the patient is sent to the operating room.

AMERICAN PHARMACEUTICAL COMPANY

Capsules Secobarbital Sodium: 0.1 Gm.

THE EVRON COMPANY, INC.

Capsules Evronal Sodium: 0.1 Gm.

GANE'S CHEMICAL WORKS, INC.

Powder Secobarbital Sodium: Bulk; for compounding use.

KEITH-VICTOR PHARMACAL COMPANY

Capsules Secobarbital Sodium: 0.1 Gm.

ELI LILLY & COMPANY

Powder Seconal Sodium: 14.1 Gm. packages for compounding use.

Powder Seconal Sodium (*Sterile*): 0.25 and 0.5 Gm. ampuls. Dry powder used to prepare a 5 per cent solution by the addition of 5 or 10 cc., respectively, of sterile distilled water.

Pulvules Seconal Sodium: 32, 50 and 100 mg.

Suppositories Seconal Sodium: A suppository containing 32.5, 65, 130 or 200 mg. of secobarbital sodium

U. S. trademark 430,202.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Capsules Secobarbital Sodium: 0.1 Gm.

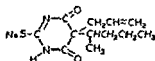
THE VITARINE COMPANY, INC.

Capsules Secobarbital Sodium: 0.1 Gm.

THIAMYLAL SODIUM.—Surital Sodium (PARKE, DAVIS).—Sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate—Thiamylal sodium is marketed as a mixture with sodium carbonate. The mixture is prepared by adding thiamylal and sodium carbonate to just

enough sodium hydroxide solution to dissolve the salts. The pH is adjusted between 10.7 and 10.9. The solution is made up to volume with water and is filtered, sterilized and lyophilized.

The structural formula of thiamylal sodium may be represented as follows.



Physical Properties—Thiamylal sodium (in admixture with sodium carbonate) consists of pale yellow, hygroscopic, agglutinated masses of crystals with no pronounced odor. It is freely soluble in water. The pH of a 2.5 per cent solution is about 10.8.

Actions and Uses—Thiamylal sodium is an ultrashort-acting barbiturate and is used particularly for intravenous anesthesia in procedures of relatively short duration. Its anesthetic potency has been found to be about 1.4 to 1.5 times that of thiopental sodium so that smaller doses are required to produce an equivalent level of anesthesia. The cumulative effect of thiamylal sodium is reported to be less than that of thiopental sodium. Its action is rapid, anesthesia generally occurs within 20 to 60 seconds and recovery may be expected within 10 to 30 minutes after the last injection, depending upon the amount of the drug administered.

Thiamylal sodium is employed intravenously as the sole anesthetic agent in relatively short surgical procedures and as a supplement to local anesthetics during regional and spinal anesthesia or for induction prior to general anesthetics during prolonged procedures. It is compatible with the use of curare drugs employed to increase surgical relaxation. Also, it is administered rectally for diagnostic procedures in children.

Thiamylal sodium is detoxified by the liver and should not be employed in patients with hepatic dysfunction or disease. It should be employed with caution in the presence of respiratory disease or obstruction, obesity, marked disturbance of arterial tension and cardiac failure or anemia. In short, this agent should be avoided whenever the intake or distribution of oxygen is impaired. It is contraindicated in traumatic shock or in conditions of impending shock.

Complications encountered are those of barbiturates in general, especially respiratory depression, hypoxia, laryngospasm, hypotension and excitement. The drug should be employed only by anesthetists familiar with the signs of anesthesia peculiar to intravenous barbiturates and the precautions in the use of these agents.

Dosage—Intravenously, an initial injection of 3 to 6 cc. of a freshly prepared 2.5 per cent solution is sufficient to produce short periods of anesthesia. The rate of injection during induction should be 1 cc. every 5 seconds, and, as indicated, additional injections of 0.5 to 1 cc. are made intermittently with the needle remaining in the vein. The maximum total dose should not exceed 1 Gm. (40 cc. of a 2.5 per cent solution). As a supplement to other forms

of anesthesia, the drug may be administered by continuous intravenous drip as either a 0.2 or 0.3 per cent solution. When preliminary medication has been given, the dosage is 0.1 to 0.2 Gm. per 45

tion is used, the dosage being based upon 0.8 to 1 Gm. per 22.7 Kg. (50 lb.) of body weight.

PARKE, DAVIS & COMPANY

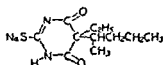
Powder Surital Sodium: 1 Gm. Steri-Vials packaged with or without diluent 0.5 and 1 Gm. ampuls packaged with diluent. 5 Gm ampuls packaged without diluent.

U. S. trademark 500,405

THIOPENTAL

Thiopentone
barbiturate—

cent of $C_{11}H_{17}N_2NaO_2S$, calculated on the dried basis." U.S.P. The structural formula of thiopental sodium may be represented as follows:



Physical Properties.—Thiopental sodium occurs as a yellowish white, hygroscopic powder and has a disagreeable odor. Its solutions are alkaline to litmus paper. It is soluble in water and in alcohol and insoluble in absolute ether, in benzene and in petroleum benzin. Its solution decomposes on standing; on boiling, precipitation occurs.

Actions and Uses.—The actions and uses of thiopental sodium are similar to those of pentobarbital sodium except that thiopental sodium is effective in smaller doses and the action is of shorter duration. When injected intravenously it is a quick-acting, general anesthetic with early recovery occasionally marked by mental depression lasting for a few hours. Intravenous use of barbiturates may be valuable, but is potentially dangerous and should be undertaken only by experts and for short operations. Facilities must be available to handle problems involving respiratory depression, laryngospasm and carbon dioxide-oxygen balance. Atropine should be administered as premedication.

Thiopental sodium also is useful for basal anesthesia by rectal administration or in conjunction with other anesthetic agents.

It is marketed by the VITARINE COMPANY, in a manner for basal anesthesia in children, in capsules for ophthalmologic and proctologic surgery.

THIAMYLAL SODIUM.—Sum of the respiratory passages, decomposed by the liver, is marketed as a mixture 2.5 per cent solution is injected intravenously. The injection then is stopped to

permit the complete effect to appear in 30 to 35 seconds. If relaxation has not occurred, an additional 2 or 3 cc. may be injected at the same rate as before.

For basal anesthesia, the rectal dosage is calculated on the basis of 1 Gm per 22.5 Kg (50 lb) of body weight or 0.2 cc. of a 10 per cent solution per pound of body weight. The solution is prepared by dissolving 3 Gm. in 30 cc. of water. Two-thirds of the calculated amount may be sufficient in obstetric cases. The preparation is administered rectally by syringe through a small catheter. The maximum total dose should not exceed 3 Gm. Soap-suds enemas should be avoided as soap apparently lessens the effect of the drug. The effect is maximal within about 30 minutes and lasts for about 1 hour. The recommended rectal dosage for preanesthetic hypnosis is 1 Gm per 34 Kg (75 lb) or 0.13 cc. of a 10 per cent solution per pound of body weight. For most surgical procedures thiopental sodium must be supplemented with another anesthetic.

Caution.—Aqueous solutions of thiopental sodium are not stable but decompose on standing; precipitation occurs when they are boiled.

ABBOTT LABORATORIES

Pentothal Sodium. 0.5 and 1 Gm vials (packaged with or without 20 and 50 cc ampuls, respectively, of water for injection) Buffered with 30 and 60 mg, respectively, of anhydrous sodium carbonate

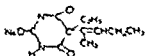
5 and 10 Gm multiple dose ampuls Buffered with 0.3 and 0.6 Gm, respectively, of anhydrous sodium carbonate

Pentothal Sodium (Rectal). 1.5 and 3 Gm vials Buffered with 0.09 and 0.18 Gm of anhydrous sodium carbonate, respectively.

Powder Pentothal Sodium. 1 Gm vials Buffered with 60 mg of anhydrous sodium carbonate

U. S. patents 2,153,729 and 2,153,731 U. S. trademark 334,342.

VINBARBITAL SODIUM-N.F.—**Delvalin Sodium** (Stear & Donatz)—Sodium 5-ethyl-5-(1-methyl-1-butenyl) barbiturate—"Vinbarbital Sodium, dried at 105° for 2 hours, yields not less than 98.3 per cent of $C_{11}H_{13}N_2NaO_3$ " N.F. The structural formula of vinbarbital sodium may be represented as follows:



Physical Properties.—Vinbarbital sodium is a white, odorless powder with a bitter taste. It is soluble in alcohol and water and slightly soluble in chloroform and ether. Unbuffered aqueous solutions of vinbarbital sodium are not stable. The powder is hygroscopic and, if capsules containing it are broken or exposed to high

humidity, the contents are affected by both moisture and carbon dioxide. A 1 per cent solution has a pH between 8.5 and 9.5.

Actions and Uses.—The actions and uses of vinbarbital sodium are similar to those of the barbitals.

for and even fall in blood pressure.

Dosage.—As a sedative, 10 to 20 mg. per day, as a sedative, 0.1 to 0.2 g. per day, must be given correspondingly smaller doses.

SHARP & DOHME, DIVISION OF MERCK & Co., INC.

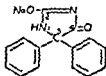
Elixir Delvinal Sodium: 473 cc. and 3.78 liter bottles. A 33 per cent alcohol elixir containing 8.33 mg. of vinbarbital sodium in each cubic centimeter.

Solution Delvinal Sodium: 5 cc ampuls and 20 cc vials. An aqueous propylene glycol solution containing 60 mg. of vinbarbital sodium in each cubic centimeter.

U. S. patents 2,119,526, 2,150,154, 2,187,701, 2,187,703 and 2,222,455
U. S. trademark 363,168

Hydantoin Derivatives

DIPHENYLHYDANTOIN SODIUM—U.S.P.—**Dilantin Sodium** (PARKE, DAVIS).—Sodium 5,5-diphenylhydantoinate—Phenytoin sodium.—“Diphenylhydantoin Sodium, dried at 105° for 4 hours, contains not less than 98.5 per cent of $C_{15}H_{11}N_2NaO_2$.” U.S.P. The structural formula of diphenylhydantoin sodium may be represented as follows:



Physical Properties.—Diphenylhydantoin sodium is a white, odorless powder. It is somewhat hygroscopic and, on exposure to air, gradually absorbs carbon dioxide with the liberation of diphenylhydantoin. It is freely soluble in water, the aqueous solution usually being somewhat turbid due to partial hydrolysis. It is soluble in alcohol but practically insoluble in ether and in chloroform.

Actions and Uses.—Diphenylhydantoin sodium is an anticonvulsant with variable or no hypnotic action. It is more effective in controlling seizures of the grand mal type than in those of petit mal. It does not affect congenital mental defects or the mental deterioration often observed in the epileptic. Proper management

of an epileptic often requires the concomitant use of several anti-convulsant drugs. Thus, phenobarbital is commonly used in conjunction with diphenylhydantoin sodium.

Side actions of varying severity include dizziness, dry skin, dermatitis, rash, itching, tremors, fever, nausea, vomiting, blurred vision, fatigue, apathy, difficult breathing and swallowing, nervousness and mental confusion with active hallucinations. Hyperplasia of the gums suggestive of scurvy may occur in young persons though its use does not interfere with the utilization of vitamin C. Diphenylhydantoin sodium is strongly alkaline, and it may give rise to gastric irritation.

Dosage.—The optimum dosage of diphenylhydantoin sodium must be determined by the daily observation of its effects on seizures and the appearance of side actions. Mild symptoms do not necessarily require that use of the drug be stopped. The beginning adult dose is 0.1 Gm. with at least half a glass of water three times daily. If necessary this dose may be increased gradually to 0.2 Gm. three times daily. Children above the age of 6 years may be given 0.1 Gm. three times daily for 1 week, after which dosage may be increased if necessary to 0.1 Gm. four times daily with at least half a glass of water to prevent gastric irritation due to alkalinity. Diphenylhydantoin sodium is effective more rapidly if given before meals, but if it causes gastric irritation it should be given immediately after meals. Children under 4 years of age may start with 0.03 Gm. mixed with cream (to disguise the bitter taste and to prevent gastric irritation) twice a day. Obviously such doses require the most careful supervision. If this dose is borne without side actions the dosage may be increased to 0.03 Gm. three or four times a day. Every slight increase in dosage is made only if necessary and if no harm is to be anticipated.

The transition from phenobarbital, bromides or other hypnotic drugs to diphenylhydantoin sodium should be made gradually, with some overlapping. By this procedure the danger of phenobarbital or bromide withdrawal symptoms (increased number of seizures) is minimized, and side actions incident to the beginning of administration of diphenylhydantoin sodium are lessened.

AMERICAN PHARMACEUTICAL COMPANY, INC.

Capsules Diphenylhydantoin Sodium 0.1 Gm.

PARKE, DAVIS & COMPANY

Kaptsale Dilantin Sodium 30 and 100 mg

Powder Dilantin Sodium 28.35 Gm vials

U. S. trademark 359,292

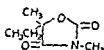
FRESKO PHARMACEUTICAL LABORATORIES, INC.

Capsules Diphenylhydantoin Sodium 30 and 100 mg

Powder Diphenylhydantoin Sodium 28, 113 and 453 Gm bottles.

Oxazolidine Derivatives

(ABBOTT).—3,5-Dimethyl-5-oxazolidinedione. The structural formula of paramethadione is:



Physical Properties.—Paramethadione is a clear, colorless liquid with an esterlike odor. It is freely soluble in alcohol, benzene, chloroform and ether and sparingly soluble in water. The pH of a saturated solution is about 6.4.

Actions and Uses.—The actions of paramethadione are similar to those of trimethadione, but the drug may be quantitatively less active. Paramethadione is indicated in the treatment of petit mal epilepsy and other conditions for which trimethadione is used.

Paramethadione is effective in a significant number of patients not benefited by trimethadione. The reverse also is true.

The side reactions resulting from paramethadione therapy are those caused by trimethadione, except that there is a lesser incidence of photophobia and rash. The most serious side effect, as with trimethadione, is severe leukopenia, which occurs occasionally; white blood cell counts, therefore, should be made bi-weekly during the first 2 months of therapy and at monthly intervals thereafter.

Dosage.—The initial dose for adults is 0.9 Gm., administered in divided doses. Thereafter, the dose should be increased or decreased to provide the smallest dose that will just control the symptoms.

For infants, the initial daily dose should be 0.3 Gm.; for children 2 to 6 years of age, 0.6 Gm. in divided doses.

ABBOTT LABORATORIES

Capsules Paradione. 0.15 and 0.3 Gm.

Oral Solution Paradione: 50 cc dropper bottles. A 65 per cent alcohol solution containing 0.3 Gm. of paramethadione in each cubic centimeter. To be diluted before administration.

U. S. patents 2,575,692 and 2,575,693 U. S. trademark 528,247

TRIMETHADIONE—U. S. P.—*Tridione* (ABBOTT).—3,5,5-Trimethyl-2,4-oxazolidinedione—"Trimethadione, previously dried over sulfuric acid for 6 hours, contains not less than 98 per cent of $C_6H_9NO_3$ " U. S. P. The structural formula of trimethadione may be represented as follows:



Physical Properties.—Trimethadione is a white, granular, crystalline substance possessing a camphorlike odor. It melts at 45 to 46.5° and is soluble in water and freely soluble in alcohol and in ether. The pH of a 5 per cent solution is about 6.0.

Actions and Uses.—Trimethadione is primarily an antiepileptic drug and has orment of epileps seizures of the better in child grand mal It organic origin forms of the sodium and/or plicated by gr has increased the number of grand mal attacks as the petit mal has decreased Combination drug therapy or readjustment of dosage may be required for optimum therapeutic effect.

Toxic reactions to trimethadione are infrequent. Gastric irritation, nausea, skin eruptions, photosensitivity and blurring of vision with a diminution in visual acuity that is reversible may be encountered and are indications for temporary withdrawal or reduction in dosage of the drug Photophobia is less frequent in children than in adults The skin manifestations that have been observed are not attributable to sensitization, and the visual disturbances have not been shown to be associated with optic nerve damage.

Rare cases of aplastic anemia with depression of all elements of the peripheral blood resulting from use of trimethadione indicate the need for repeated complete blood examinations of patients receiving this drug It has been suggested that small initial doses be used and the patient cautioned to report at once any untoward symptoms that ensue Careful medical supervision of patients under treatment with trimethadione is essential It should not be used in the presence of anemia, leukopenia or thrombocytopenia and employed with caution if at all in blood dyscrasia.

It is contraindicated in patients with advanced renal or hepatic disease or with disease of the optic nerve

Dosage.—In petit mal epilepsy, the dosage required may vary from 1 to 2 Gm daily, given in divided doses of 0.3 Gm three to seven times per day In children under 6 years of age it is advisable to begin with 0.15 to 0.3 Gm three times daily and to increase this if necessary Optimum dosage must be determined for each patient Weekly, and later monthly, leukocyte counts should be made Tablets of the drug are compounded with an appreciable amount of magnesium trisilicate as an absorbent Large quantities of such tablets are contraindicated for children for whom a ketogenic diet has been prescribed

ABBOTT LABORATORIES

Capsules Tridione: 0.3 Gm

Dulcet Tablets Tridione: 0.15 Gm

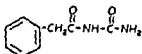
U. S. patents 2,575,692 and 2,575,694 U. S. trademark 40,527 (Dulcet)

Solution Tridione: 473 cc. and 3.78 liter bottles. A solution containing 40 mg. of trimethadione in each cubic centimeter.

U. S. trademark 300,401.

Phenylacetylurea

PHENACEMIDE.—Phenurone (ABBOTT).—Phenylacetylurea—The structural formula of phenacemide may be represented as follows:



Physical Properties.—Phenacemide is a white to creamy white, crystalline powder, melting at 117° and 116°.

with only minor sedative action. In experimental animals the drug shows effectiveness against electroshock seizures and convulsions. Large doses produce marked ataxia.

aplastic anemia, have followed administration of the drug. It should be employed only by physicians experienced in the treatment of epilepsy and only in patients whose seizures are difficult or impossible to control with other recognized anticonvulsants.

Phenacemide should not be employed in patients with evidence of liver dysfunction and should be used with caution in patients with histories of personality disorders or sensitivity to drugs. It may be advisable to hospitalize such patients for observation during the first weeks of treatment. Psychiatric signs such as withdrawal and loss of interest indicate onset of serious personality changes. Careful clinical observation throughout the course of therapy is especially important during the first 6 months, the first symptoms as anorexia, rash or jaundice, as they blood dyscrasia. Anorexia, gastro-intestinal distress, resistant may be of more serious significance. Patients

terminated according to the response of control already obtained with other anticonvulsant agents.

may be given in conjunction with phenobarbital, diphenylhydantoin sodium, trimethoprim, etc., that when some of these are used this should be 0.5 Gm three times daily, increased gradually to the minimum required for adequate control or until limiting side effects develop. The action of an average dose appears to last for 3 to 5 hours. If control by phenacemide alone is anticipated, other medication can be reduced, but if a combination of phenacemide with other drugs permits better control, or allows control with lower dosage of phenacemide or less disturbing side effects, the combination of medication should be continued. Doses as small as 0.25 Gm three times daily may be adequate in some cases. The average total daily adult dose seldom exceeds 2 to 3 Gm. For children 5 to 10 years of age, approximately half the adult dose is recommended. The maintenance dose should be the smallest amount that will adequately control seizures. Personality disturbances, signs of liver damage, rash or depression of the blood count, particularly of erythrocytes and polymorphonuclear leukocytes, are indications for withdrawal. Cautious reinstitution of therapy may be considered when improvement occurs.

ABBOTT LABORATORIES

Tablets Phenurone: 0.5 Gm.

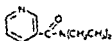
Enterab Tablets Phenurone: 0.3 Gm

U. S. trademarks 532,257 and 353,674 (Enterab)

CENTRAL NERVOUS SYSTEM STIMULANTS

Several drugs are used occasionally as central nervous system stimulants, particularly as respiratory stimulants when the respiratory mechanism fails to respond to normal stimulation, as with carbon dioxide. The weakest and safest of these is caffeine; nikethamide is intermediate, pentylenetetrazole (metrazol) and picrotoxin are the most potent. However, this group has few indicated uses except in the treatment of barbiturate intoxication, although the administration of oxygen, gastric lavage, artificial respiration and maintenance of an airway may be more effective measures.

NIKETHAMIDE-U.S.P. — N,N-Diethyl-3-pyridinecarboxamide. — N,N-Diethylnicotinamide. — The structural formula of nikethamide may be represented as follows:



Physical Properties — Nikethamide occurs as a clear, colorless to pale yellowish, somewhat viscous liquid, which crystallizes on

standing in the cold and melts again as the temperature rises. It has a faint, characteristic, aromatic odor and a peculiar, bitter taste. Its solutions are clear and nearly colorless and have no more than a faint odor of diethylamine. It is miscible with water, with alcohol and with ether.

Actions and Uses.—Nikethamide acts mainly on the central nervous system. It stimulates medullary centers, increasing the rate and depth of respiration and causing peripheral vasoconstriction. Respiration also is stimulated through action on the chemoreceptors of the carotid body. In animals its administration usually results in some increase in blood pressure, but this may be preceded by a sudden temporary lowering of the pressure. Nikethamide sometimes raises blood pressure in human beings, but apparently the vasomotor center can be stimulated only under certain circumstances. Rise in blood pressure may be secondary to improved respiration and to stimulation of the reflex centers. Small doses in experimental animals exert no action on the coronary vessels, but larger doses may increase the coronary flow. However, clinical evidence for the use of nikethamide to promote increased coronary blood flow is not conclusive.

Nikethamide has been used clinically as a cardiac stimulant, but it is not especially efficient and the cardiac effect probably depends on action on respiration rather than on the myocardium. The analeptic action of nikethamide suggests its usefulness in combating acute respiratory depression from anesthetics, alcoholic intoxication and hypnotics. However, it is not clear that nikethamide is superior in this respect to other available drugs, especially in cases of barbiturate poisoning. Because of its additional action on peripheral vascular tone it is beneficial in acute circulatory failure occurring during surgical procedures or pneumonia. However, nikethamide is contraindicated in pneumonia unless circulatory collapse supervenes.

Dosage.—Nikethamide is available as an aqueous solution, 25 per cent W/V, for oral and for subcutaneous, intramuscular or intra-

..... ration.
..... amide
..... dose

depends on the rate of injection. When doses larger than 3 cc. are given, the administration should be slow and the general reaction of the patient should be watched. Large or toxic doses produce convulsions and may cause death from respiratory failure. The dose may be repeated at intervals according to the needs of the patient.

BUFFINGTON'S, INC.

Solution Nikethamide 25%: 2 and 5 cc. ampuloids. A solution containing 0.25 Gm. of nikethamide in each cubic centimeter.

THE DRUG PRODUCTS COMPANY, INC.

Solution Nikethamide 25%: 15 cc. ampuls and 30 cc. vials A

solution containing 0.25 Gm of nikethamide in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

ENDO PRODUCTS, INC.

Solution Nikethamide 25%: 1.5 and 5 cc. ampuls and 15 cc. vials for oral administration. A solution containing 0.25 Gm of nikethamide in each cubic centimeter.

E. S. MILLER LABORATORIES

Solution Nikethamide 25%: 1.5 and 5 cc. ampuls. A solution containing 0.25 Gm. of nikethamide in each cubic centimeter.

PRESO PHARMACEUTICAL LABORATORIES

Solution Nikethamide 25%: 60 and 480 cc bottles for oral administration. A solution containing 0.25 Gm. of nikethamide in each cubic centimeter.

Solution Nikethamide 25%: 1.5 cc. ampuls. A solution containing 0.25 Gm of nikethamide in each cubic centimeter.

THE UPJOHN COMPANY

Solution Nikethamide 25%: 1.5 cc. ampuls, 10 cc. vials and 88.7 cc bottles. A solution containing 0.25 Gm. of nikethamide in each cubic centimeter.

PICROTOXIN-N.F.—Cocculin—"Picrotoxin is an active principle obtained from the seed of *Anamirta Cocculus* (Linné) Wight et Arnott (Fam. Menispermaceae)." N.F.

Physical Properties.—Picrotoxin occurs as flexible, shining, prismatic crystals or as a microcrystalline powder. It is odorless and stable in air but is affected by light. One gram of picrotoxin dissolves in about 350 cc of water at 25°, in about 5 cc. of boiling water and in about 3 cc. of boiling alcohol. It is more readily soluble in diluted acids and alkalis. It is sparingly soluble in ether and in chloroform.

Actions and Uses.—Picrotoxin is a stimulant and convulsant that acts chiefly on the higher centers. Thus if the midbrain and

body

Dosage.—In cases of barbiturate poisoning, 6 mg should be administered intravenously, and the dose should be increased by 3 mg.

increments at 15-minute intervals up to a total of 15 mg. or until the desired response is obtained. The interval between injections is important because there is a latent period between the injection and the manifestation of the full effect of the drug; failure to allow for this may lead to overdosage. Artificial respiration, an open airway, oxygen, gastric lavage and intravenous fluids should be employed concurrently with the picrotoxin therapy. An intravenous barbiturate always should be on hand to combat any incidental overdosage of picrotoxin.

ABBOTT LABORATORIES

Solution Picrotoxin 0.3%: 20 cc vials. An isotonic sodium chloride solution containing 3 mg. of picrotoxin and 0.9 per cent benzyl alcohol in each cubic centimeter.

Contraceptives

When protection from pregnancy is considered advisable, contraceptives are used to prevent passage of active spermatozoa from the vagina into the uterus. Whenever protection is important, occlusive devices such as diaphragms are used, reinforced by contraceptive jellies or creams. Diaphragms cannot be expected to prevent the passage around their rim of so small a body as the sperm. They make it necessary, however, for these cells, which otherwise may be deposited in immediate contact with the os, to travel 60 to 100 mm (12,000 to 20,000 body lengths) before reaching the cervical mucus. The duration of exposure to the contraceptive material is increased greatly thereby and the effectiveness of the procedure heightened. Contraceptive jellies and creams act as chemical agents, immobilizing the spermatozoa with which they come into contact. Because of their consistency they also have an obstructive function. Accessory devices used in contraception are inserters and extractors for the diaphragms, and syringe applicators for the jellies and creams. In control of conception acceptability of the prescription probably plays a greater role in use and, therefore, effectiveness than in most fields of medicine. A perfume pleasing to the users, and a degree of lubrication suited to their needs also may prove important factors in contraceptive success. The esthetic block against various methods differs with the user, and variation of method by a single user often leads to greater acceptability and consequently to a higher degree of protection.

When contraceptive preparations are prescribed, the physician should warn that only by strict adherence to his directions can the maximum effect be obtained. No one method can be guaranteed 100 per cent effective, although a high degree of protection can be expected if the patient has been properly examined and informed by the physician. It is difficult to make exact comparisons of the effectiveness of different contraceptive methods or materials. Errors in technic often are not recognized, semen may reach the genitalia at detumescence or removal of the condom, tears may not be noticed, and diaphragms may be placed in front of the cervix, affording no protection to the os. Most difficult to estimate are the errors of omission which occur when couples decide not to bother with the contraceptives "just this once" yet hesitate to report their responsibility for the "failure" by omitting from the computation pregnant contraceptors who admitted that they had been negligent, and by including those who were equally negligent but did not conceive, unjustifiably high estimates of protection have been secured.

Spermicidal times are used to determine the comparative effec-

tiveness of contraceptive mixtures, but the circumstances of the determinations do not duplicate those of clinical use. The Brown and Gamble test employed as one of the criteria for acceptance (see the section on evaluation of certain products) requires complete mixing, which is not present clinically, and dilution to a degree that may be greater than that in the vagina. This test, however, furnishes one indication of the qualities required in contraceptives and is, perhaps, less subject to error than the test of clinical use. A description of the method and the results of its application to commercial contraceptive materials secured in 1949, was published in *J.A.M.A.*, 148:50 (Jan. 5) 1952.

The status of conception control has been reviewed in a report of the Council which appeared in *J.A.M.A.*, 123:1043 (Dec. 18) 1943.

For the Council's criteria for acceptance of contraceptive agents, see section on evaluation of certain products.

APPARATUS FOR USE WITH CONTRACEPTIVES

Criteria for acceptance, and acceptance of contraceptive diaphragms and accessory devices, such as inserters and extractors, are in the purview of the Council on Physical Medicine and Rehabilitation. In *New and Nonofficial Remedies*, accepted apparatus are listed with the contraceptives with which they are used. For detailed descriptions, see "Apparatus Accepted," published by the Council on Physical Medicine and Rehabilitation.

Diaphragms listed below usually are supplied by the manufacturer in diameters differing by 5 mm. from about 55 mm. to about 100 mm.

Applicators listed below are transparent plastic syringes threaded at the blunt intravaginal end to screw onto the tubes of jelly or cream to permit filling by compression of the tube. The full capacity of the applicators (unless otherwise stated) is 5 cc., the recommended dose.

JELLIES AND CREAMS

Actions, Uses and Dosage.—Jellies and creams for contraceptive use usually are introduced into the vagina on the occlusive diaphragm or cervical cap with which they are used. This agent should be introduced not more than 12 hours before sexual intercourse. A portion of the dose of jelly or cream is placed on the rim of the occlusive device, the balance on the upper side, the side that will be in contact with the cervix. A few physicians recommend the subsequent introduction of additional jelly or cream close to the occlusive device by means of a syringe applicator.

Jellies and creams also may be used without an occlusive device,

When introduced separately.
The recommended dose varies but usually is 5 cc.

5 cc. To allow adequate time for the chemical to immobilize the spermatozoa, the occlusive device should not be removed nor should a douche be taken within 6 hours of ejaculation.

As most of the contraceptive diaphragms are made of rubber which will deteriorate if exposed to greases, the jellies and creams used should not contain greasy substances, such as lanolin or petrolatum.

Applicators are designed for ready filling from the container of contraceptive jelly or cream and for delivery of the recommended dose under moderate pressure into the upper vagina. Applicator should be transparent, to permit detection of air which might lead to inadequate dosage, and, if made of glass, should be sufficiently thick walled to prevent breaking in the vagina. The end should be blunt and sufficiently large to prevent entry into the urethra.

CONTRA COMPANY, DIVISION OF SLEVINA LABORATORIES, INC.

Contra Creme: 63.5 Gm collapsible tubes. A stearic acid cream having a pH of 7.3, packaged from the formula:

	Per Cent
Phenylmercuric acetate	0.06
Stearic acid	12.0
Triethanolamine	0.66
Glycol monostearate	3.5
Glycerin	2.5
Distilled water to make	100.00

U. S. trademark 333,838

Contra Applicator and Contra Diaphragm: See the general statement on apparatus for use with contraceptives.

DUREX PRODUCTS, INC.

Lactol Creme: 78 and 116 Gm collapsible tubes. A water-dispersible, nonfatty stearic acid and glyceryl monostearate cream, having a pH of 6.5, prepared from the formula:

	Per Cent
Glyceryl monoricinoleate	1.50
Lactic acid	0.10
Sodium lauryl sulfate	0.60
p-Triisopropylphenoxypolyethoxyethanol	1.25
Stearic acid	15.00
Glyceryl monostearate	7.50
Glycerin	8.00
Perfume	0.07
Water sufficient to make	100.00

U. S. patent 2,467,834

Lactol Jelly: 85 and 128 Gm collapsible tubes. A water-soluble jelly formed from tragacanth, karaya and acacia, having a pH of 4.1, prepared from the formula:

	Per Cent
Glyceryl monoricinoleate	1.00
Lactic acid	1.50
Sodium lauryl sulfate	0.25
Hydroxyquinoline sulfate	0.05
Butyl p-hydroxyphenylate	0.50
p-Triisopropylphenoxypolyethoxyethanol	1.25

Sodium chloride	6 00
Glycerin	3 00
Tragacanth	2.70
Karaya	1.00
Acacia	1.00
Perfume	0 04
Water sufficient to make	100.00

U. S. patent 2,467,884.

Lactikol Metri-Dose Applicator: Fitted at the distal end with a rubber compression bulb with central wire spring device to permit adjustment of the volume of jelly or cream to be delivered between 5 and 8 cc.

U. S. patent 2,224,018

Lactikol Plunger Applicator and Durex Diaphragms, Diaphragm Introducer and Fitting Rings: See the general statement on apparatus for use with contraceptives.

EATON LABORATORIES

Lorophyn Jelly: 92 Gm. collapsible tubes. A water-soluble jelly formed from tragacanth and purified Irish moss, having a pH of 7.5, prepared from the formula:

	Per Cent
Phenylmercuric acetate ..	0 05
Polyethylene glycol of monoisooctyl phenyl ether ..	0.5
Sodium borate-U.S.P.	3 0
Methylparaben ..	0 05
Gum tragacanth ..	1.8
Purified Irish moss ..	0 72
Glycerin ..	8 0
Water sufficient to make ..	100.00

U. S. patent 2,416,184 U. S. trademark 417,240

Lorophyn Jelly Applicator: See the general statement on apparatus for use with contraceptives.

ESTA MEDICAL LABORATORIES, INC.

Lanteon Jelly: 42.5 and 85.35 Gm collapsible tubes. A water-dispersible jelly having a pH of 5.2, prepared from the formula.

	Per Cent
Ricinoletic acid ..	0.50
Hexylresorcinol ..	0.10
Sodium benzoate ..	0 20
Chlorothymol ..	0.00769
Gum tragacanth ..	1 73
Starch ..	0.97
Hydrochloric acid ..	0 043
Calcium hydroxide ..	0 0264
Perfume ..	0 0126
Water sufficient to make ..	100 00

Lanteon Applicator and Lanteon Flat Spring Meninga Type Diaphragm: See the general statement on apparatus for use with contraceptives.

HOLLAND-RANTOS COMPANY, INC.

Koromex Cream: 78, 113 and 155 Gm. collapsible tubes. A water-

soluble stearic acid emulsion having a pH of 4.2 to 4.4, prepared from the formula:

	Per Cent
Phenylmercuric acetate	0.02
Boric acid	2.0
Hydroxyquinoline benzoate	0.02
Cetyl alcohol	1.0
Stearic acid	20.0
Butyl <i>p</i> -hydroxybenzoate	0.02
Sorbitan monooleate	5.0
Polyoxyalkylene sorbitan monostearate	3.0
Glycerin	5.0
Perfume	0.015
Water sufficient to make	100.00

U. S. trademark 213,756.

Koromex Jelly: 85, 128, and 142 Gm collapsible tubes. A water-soluble jelly formed from tragacanth and gum acacia having a pH of 4.6, prepared from the formula

	Per Cent
Phenylmercuric acetate	0.02
Hydroxyquinoline benzoate	0.02
Boric acid	2.0
Butyl <i>p</i> -hydroxybenzoate	0.02
Glycerin	10.0
Gum acacia	0.6
Tragacanth	2.5
Perfume	0.015
Water sufficient to make	100.00

U. S. trademark 213,756

Koromex Vaginal Applicator and Koromex Diaphragm: See the general statement on apparatus for use with contraceptives.

LEHY & FINE PRODUCTS CORPORATION

Lygel Vaginal Jelly 92 Gm collapsible tubes. A water-soluble jelly having a pH of 3.4, prepared from the formula:

	Per Cent
Benzalkonium chloride	0.10
Lactic acid	0.25
<i>p</i> -Chloro- <i>o</i> - <i>m</i> -xyleneol	0.05
<i>p</i> -tert.-Amylphenol	0.05
Glycerol	15.00
Gum tragacanth	2.50
Pectin	1.00
Perfume oil	0.10
Water sufficient to make	100.00

U. S. trademarks 343,141 and 348,042

Lygel Vaginal Applicator: See the general statement on apparatus for use with contraceptives.

U. S. patents 1,918,706, 2,077,176, 2,161,178 (applicator).

ORTHO PHARMACEUTICAL CORPORATION

Ortho-Creme Vaginal Cream: 78 and 121 Gm collapsible tubes. A nonfatty stearic acid cream having a pH of 5.5 to 5.9, prepared from the formula:

	Per Cent
Ricinoleic acid	0.75
Cetyl alcohol	0.50
Sodium lauryl sulfate	0.28
Boric acid	2.00
Triethanolamine	0.25
Stearic acid	24.00
Glycerin	8.00
Perfume	0.05
Water sufficient to make	100.00

U. S. patent 2,330,846. U. S. trademark 390,141.

Ortho-Gynol Vaginal Jelly: 85 and 142 Gm. collapsible tubes. A water-soluble jelly formed from tragacanth and acacia, having a pH of 4.5, prepared from the formula:

	Per Cent
Ricinoleic acid	0.70
Glacial acetic acid	0.33
Hydroxyquinoline sulfate	0.025
Boric acid	3.00
Diisobutylphenoxypolyethoxyethanol	1.00
Propylparaben	0.05
Glycerin	5.00
Acacia	0.53
Tragacanth	3.00
Perfume	0.025
Water sufficient to make	100.00

The consistency is indicated by a 50 to 55 mm. dart penetration at 40° when tested with the Braun dart penetrometer.

U S patents 2,330,846 and 2,541,103 U S trademark 298,222.

Ortho Vaginal Applicator and Ortho Diaphragm and Ortho Diaphragm Introducer: See the general statement on apparatus for use with contraceptives.

U S. trademark 394,998 (applicator).

JULIUS SCHUMM, Inc.

Ramses Vaginal Jelly. 85 and 143 Gm collapsible tubes A water-soluble jelly formed from carboxymethylcellulose and glycerin, having a pH of 4.5, prepared from the formula.

	Per Cent
Boric acid	1.00
Dodecaethylene glycol monolaurate	5.00
Alcohol	5.00
Butyl p-hydroxybenzoate	0.02
Carboxymethylcellulose sodium	2.50
Glycerin	7.00
Perfume	0.01
Water sufficient to make	100.00

U S patents 2,467,884 and 2,623,840 U S. trademarks 306,696 and 401,369

Ramses Vaginal Applicator and Ramses Diaphragm, Diaphragm Introducer and Fitting Rings. See the general statement on apparatus for use with contraceptives

U S trademarks 284,083 (diaphragm), 353,028 (introducer) and 580,812 (applicator).

TABLEX COMPANY

Mervosan Cremet 70.8 Gm. collapsible tubes. A stearic acid cream having a pH of 7.45, prepared from the formula:

	Per Cent
Paraformaldehyde	0.1
Triethanolamine	1.96
Methylparaben	0.1
Propylparaben	0.1
Propylene glycol	5.4
Glycerin	6.3
Sodium oleate	0.5
Stearic acid	29.8
Perfume	0.07
Water sufficient to make	100.00

U. S. trademark 278,907.

Mervosan Applicator: See the general statement on apparatus for use with contraceptives.

VERITAS PRODUCTS COMPANY, INC.

Veritas Krema: 70.8 and 134.6 Gm. collapsible tubes. A stearic acid cream having a pH of 7.45, prepared from the formula:

	Per Cent
Paraformaldehyde	0.1
Triethanolamine	1.96
Methylparaben	0.1
Propylparaben	0.1
Propylene glycol	5.4
Sodium oleate	0.5
Stearic acid	29.8
Glycerin	6.3
Perfume	0.07
Water sufficient to make	100.00

Veritas Applicator and Veritas Plunger Applicator: See the general statement on apparatus for use with contraceptives.

WHITTAKER LABORATORIES, INC.

Cooper Crema. 75 Gm. collapsible tubes. A white, nongreasy, water-miscible stearate cream having a pH of 7.3 prepared from the formula

	Per Cent
Trioxymethylene	0.04
Diethyl sodium sulfosuccinate	0.10
Hydrous aluminum silicate	2.34
Trihydroxyethylamine	7.91
Sodium oleate	0.67
Stearic acid	23.04
Perfume (compounded oil of lavender)	
Water sufficient to make	100.00

Cooper Crema Dosimeter (full capacity is 10 cc) and **Cooper Latex Diaphragm:** See the general statement on apparatus for use with contraceptives.

CAPSULES AND SUPPOSITORIES

Actions and Uses.—Capsules and suppositories provide a convenient method for introducing obstructive and spermicidal ma-

terial into the vagina with the advantage of freedom from the need of apparatus. The solid material introduced must be converted to a jelly or liquid form in order to cover the requisite area; hence prompt liquefaction is important. In some suppositories this results from a melting point below the temperature of the body. In others the active material is enclosed in a gelatinous shell which melts or opens when exposed to body temperature and moisture. The time required should be under 10 minutes and users should allow at least 15 minutes to elapse before intercourse. A douche should not be taken for at least 6 hours after ejaculation.

To ensure further protection, physicians should advise the concurrent use of an occlusive device such as a diaphragm, and should stress the fact that suppositories or capsules used alone are less effective. If adequate time is allowed for liquefaction, the protection afforded should equal that of jelly or cream used without an occlusive device.

EATON LABORATORIES

Lorophyn Suppositories: A vaginal suppository hermetically sealed in foil consisting of a water-dispersible, low-melting mass prepared from the formula:

	Per Cent
Phenylmercuric acetate	0.02
Methylbenzethonium chloride	0.20
Methylparaben	0.10
Sorbitan sesquioleate	5.00
Polyoxyethylene palmitate	14.68
Polyethylene glycol 1000	80.00

Dosage.—One suppository, containing 2 Gm.

U. S. trademark 417,240.

LEHN & FINK PRODUCTS CORPORATION

Lygenes Vaginal Suppositories: A vaginal suppository with an oil of theobroma base prepared from the formula:

	Per Cent
Zinc phenosulfonate	0.50
Hydroxyquinoline benzoate	0.30
p-Chloro- <i>sym.</i> - <i>m.</i> -xyleneol	0.05
p- <i>tert.</i> -Amylphenol	0.05
Boric acid	0.10
Beeswax, white	5.00
Corn starch	9.00
Perfume	0.20
Cocoa butter	84.80

Dosage.—One suppository, containing 2.25 Gm.

Diagnostic Aids

In this chapter are assembled drugs that help to reveal the anatomic evidences of disease or that furnish a physiologic test of renal or hepatic function. The list includes compounds used as contrast media in roentgenography and used in testing the functional capacity of the kidneys and liver.

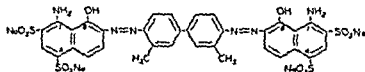
Allergic extracts used for diagnosis are exempted from inclusion in *N.N.R.* For reference to products formerly included, see *N.N.R.* 1950. Toxins used in immunity tests are described in the chapter on serums and vaccines. Neostigmine and edrophonium, used in the diagnosis of myasthenia gravis, are described elsewhere—the former in the chapter on autonomic drugs, the latter in the chapter on skeletal muscle relaxants and their antagonists. Sodium radioiodide (I^{131}), used in the diagnosis of thyroid disease, is described in the chapter on radioactive isotopes.

Agents Used for Determination of Blood Volume

EVANS BLUE-U.S.P.—Tetrasodium salt of 4,4'-bis(2,4,6-trihydroxy-3-sulfamoylphenyl)azobenzene.

Chemical structure

This dye may be represented as follows:



Physical Properties.—Evans blue is a bluish green or brown iridescent powder. It is very soluble in water, very slightly soluble in alcohol and practically insoluble in benzene, carbon tetrachloride and ether. The pH of a 0.5 per cent solution is between 5.5 and 7.5.

Actions and Uses.—Evans blue is a diazo dye that, when injected into the blood stream, combines firmly with plasma albumin and leaves the circulation very slowly. Its optical density is directly proportional to its concentration.

Evans blue is useful as an intravenous diagnostic agent for the colorimetric determination of blood volume by the plasma-dye-

hematocrit method. Although the technic of the test is difficult, it gives good results when performed properly. The normal value for blood volume varies with body weight and hematocrit and cannot be stated specifically. The value for men tends to be higher than for women.

Determination of blood volume is important in the detection of impending shock. It is also important as a guide to the amount of blood, plasma or other fluids needed to avoid inadequate or excessive dosage in conditions accompanied by decreased blood volume. Such requirements also are estimated for the preoperative and postoperative management of chronically ill or debilitated patients. The use of the dye by other routes of administration or for other purposes is still in the experimental stage.

Mixing of the dye with the blood in normal persons usually is complete 9 minutes after intravenous injection; however, in patients with congestive heart disease or in severe shock, the mixing time may be prolonged to 15 minutes. The dilution of the dye in blood withdrawn serves as a quantitative indication of the volume of total circulating plasma when compared colorimetrically with the plasma of the patient before injection.

The exact final disposition of the dye in the body is not known. It is removed from the vascular system chiefly by diffusion via the capillaries into the extravascular tissues. Small amounts are excreted in the bile and also are taken up by wandering phagocytic cells. Apparently, it is not excreted in the feces and does not pass into the cerebrospinal fluid or through the placenta, and is not known to appear in the urine of patients with undamaged kidneys. Acute or chronic toxic effects have not been reported following clinical use of doses required for determination of blood volume. With doses several times greater than necessary, blue staining of the skin and sclerae occurs. Studies in animals indicate that the chief danger from high doses is the production of pulmonary emboli or lesions of the lungs. Such effects have not been observed in human beings.

Dosage.—Evans blue is administered intravenously with the patient in the fasting state (to avoid lipemia) and under approximate basal conditions, including recumbency for at least 15 minutes prior to the test. The dosage consists of a single injection, into the antecubital vein, of 25 mg. of dye as 5 cc. of a 0.5 per cent aqueous solution which has been diluted further with 1 to 2 cc. of isotonic sodium chloride solution. Before the dye is administered, about 10 cc. of blood is withdrawn. The tourniquet must be released promptly to avoid venous stasis which results in inaccuracy of the hematocrit value. The dye then is injected cautiously to avoid extravasation and local staining of the perivascular tissues. The syringe should be rinsed with blood several times to ensure complete administration of the dye. Exactly 10 minutes after beginning the injection (15 minutes in acute shock or cardiac decompensation) a second 10 cc. sample of blood is withdrawn from the antecubital vein of the opposite arm, again with care to avoid undue stasis. Each sample is placed immediately on withdrawal into several 4 cc. hematocrit tubes containing 1 mg. of dried heparin

sodium per tube to prevent coagulation. When gross hemolysis or lipemia of the plasma cannot be avoided, an extraction method should be employed. Other tests desired may be performed on the undyed sample. The hematocrit tubes are centrifuged at 3,000 rpm with a radius of 15 cm to determine the hematocrit. Samples of the dye-tinged and dye-free plasma then are separated from the tubes for comparison with a properly calibrated photometer. With any one manufacturer's lot of dye it is necessary to calculate the optical density of a 1:500 dilution of the dye in normal dye-free plasma when a 1 cm cuvette is used for readings (otherwise the dilution is in proportion to the size used). The volumes of the blood components are calculated in accordance with the following formulas.

1. Total plasma vol. = $\frac{[\text{ml of dye solution injected (5 ml)} \times \text{dilution of standard (500)} \times \text{optical density of a standard}]}{\text{optical density of dye-tinged plasma (unknown)}}$
2. Total blood vol = Total plasma vol \div $1 - (0.96 \times \text{hematocrit})$
3. Red cell vol = Total blood vol $-$ Total plasma vol.

Normal values are estimated on the basis of normal body weight (in Kg) of the patient when healthy. Experiments on men of average build indicate normal values as follows:

1. Plasma vol in cc = Wt in Kg \times 45
2. Blood vol. in cc = Wt in Kg \times 85
3. Red cell vol in cc = Wt in Kg \times 40

Values for women usually are somewhat lower.

WARNER-CHILCOTT LABORATORIES, DIVISION OF WARNER-HORVAT, INC.

Solution Evans Blue: 5 cc ampuls. An aqueous solution containing 5 mg. of Evans blue in each cubic centimeter. Packaged with 5 cc ampuls of normal saline solution.

Agents Used for Determination of Gastric Acidity

QUININE CARBACRYLIC RESIN — *Diagnee* (Squibb). — The quinine salt of a polyacrylic carboxylic acid resin containing about 1.85 per cent of quininium ion.

Physical Properties. — Quinine carbacrylic resin is a buff, odorless, tasteless, free-flowing, amorphous, granular solid. It is practically insoluble in dilute acids and alkalis, alcohol, ether and water.

Actions and Uses. — Quinine carbacrylic resin, a complex of quininium ion and carbacrylic resin, is employed as an indicator for the detection of gastric anacidity (achlorhydria) without intubation. After oral administration of the drug, the quinine in the resin is displaced by the hydrogen ions of free hydrochloric acid that may be present in the stomach. Approximately 1 per cent of the displaced quinine is excreted in the urine within 2 hours following administration of the resin. A stimulant to gastric secre-

tion is given 1 hour before administration of the resin. Urine voided during that hour serves as a control sample. Assay of the quinine content of urine specimens, collected at the end of the 1-hour control period and 2 hours after administration of the resin, is performed as an indication of the presence or absence of free hydrochloric acid in the stomach.

Assay of the urine for quinine is based on the measurement of its fluorescence in aqueous extract under ultraviolet light. Estimation of the urinary quinine level by this method may be carried out with a photoelectric fluorophotometer for direct calculation from a predetermined standard curve or by visual comparison with freshly prepared standard solutions containing known amounts of quinine. If the fluorescence of the control sample corresponds to 15 mcg or more of quinine, the entire test should be disregarded. It indicates that the patient is excreting excessive amounts of blank fluorescent materials which may result from the use of quinine or related drugs or vitamins of the B-complex or the steroid compounds. The use of any such medication should be discontinued for 1 week and the test repeated. If the result from the control sample corresponds to 5 to 15 mcg of quinine, the result from the test specimen should be corrected by subtracting the amount found in the control. If the amount in the control is less than 5 mcg, it may be ignored. The interpretation of the absence or presence of free gastric hydrochloric acid is as follows: Free gastric hydrochloric acid is absent if 15 mcg. of quinine or less is excreted in the 2-hour urine specimen. Free gastric hydrochloric acid is present if more than 15 mcg. of quinine is excreted in the 2-hour urine specimen. A range of quinine between 15 and 30 mcg signifies a low degree of gastric acidity.

The quinine carbacrylic resin test does not furnish exact quantitative results; however, it is convenient for screening patients with minor gastric symptoms that are not considered sufficiently significant to warrant the discomfort of intubation gastric analysis or other more expensive diagnostic procedures. It should not be employed in lieu of more extensive examinations whenever these may be indicated. Until the physician has acquired experience with the resin method, doubtful results should be confirmed by repetition of the test after an interval of 5 to 7 days. The resin test method for achlorhydria is considered useful for the diagnosis of suspected cancer of the stomach, pernicious anemia and gastric polyps.

Quinine carbacrylic resin is given to patients

Dosage.—Quinine carbacrylic resin
single test dose of 2 Gm.
given the test should be repeated
ceding the day of the test

The contents of a 0.25 Gm. capsule is stirred and taken in another one-half glass of water, cream, milk or sugar. One hour

later or as soon thereafter as is possible, the patient voids and saves this specimen in a bottle marked "urine control." Then the 2 Gm. dose of the resin is stirred well and taken in one-fourth glass of water (without chewing the granules), followed by another one-fourth glass of water. Exactly 2 hours after taking the resin, the urine should be voided and the entire amount saved in a bottle marked "urine sample." The bladder should be emptied completely each time, if urination ahead of the scheduled time is necessary, it should be added to that passed at the end of the designated period. After the last specimen is completed, the patient may eat breakfast. The two specimens should be delivered to a clinical laboratory as soon as it is convenient.

If desired, an injection of histamine phosphate may be used in place of oral caffeine as a stimulant to gastric secretion and the control specimen collected after a 45-minute period.

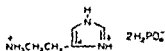
E. R. SQUIBB & SONS, DIVISION OF OLIN MATTHEWSON CHEMICAL CORPORATION

Granules Diagnox: A quininium indicator resin, each test containing a 2 Gm. packet of quinine carbacrylic resin and a 0.25 Gm. capsule of caffeine and sodium benzoate.

U. S. trademark 368,004

Agents Used for Testing Gastric Secretory Activity

HISTAMINE PHOSPHATE-U.S.P.—Histamine Acid Phosphate—The structural formula of histamine phosphate may be represented as follows:



Physical Properties—Histamine phosphate occurs as colorless, odorless, long prismatic crystals. It is stable in air but is affected by light. Its solutions are acid to litmus paper. One gram of histamine phosphate dissolves in about 4 cc. of water.

Actions and Uses—Histamine exists in various organs and tissues of the body, probably in an inert form. It produces local vasodilatation when released from the cell under appropriate stimuli, such as trauma, shock and, possibly, allergic reactions. When injected into an animal, histamine stimulates gastric secretion and produces flushing, nausea, bronchospasm, fall in blood pressure, arrhythmia and gastro intestinal contraction. It acts directly on the receptive substance in smooth muscle.

Histamine, although absorbed orally, produces highly variable effects when administered by this route. Salts of histamine usually are administered subcutaneously, intravenously or intramuscularly.

Histamine phosphate is employed as a test for gastric secretory activity. It also produces a temporary benefit in some patients with Menière's syndrome, including those showing sudden deafness. It

has been used in the treatment of multiple sclerosis; although the effects are equivocal, they deserve further study. Some patients apparently experience temporary amelioration of the disease after histamine therapy.

Although histamine has been recommended for treatment of migraine and certain cephalgias, the evidence of value is not convincing. Because of the known hazards of histamine therapy, the drug should not be used indiscriminately in these conditions.

Histamine is a potent drug, and overdosage or administration to susceptible persons may give rise to serious reactions. Vasomotor collapse, shock and even death may occur quickly if the drug is administered too rapidly or in too great a quantity. Thus, when calculating dosages, it should be remembered that the salt contains only about 36 per cent of the active base. Epinephrine hydrochloride is the antidote of choice in histamine overdosage and should be given intramuscularly or, in severe poisoning, intravenously. A solution of epinephrine hydrochloride 1:1,000 always should be readily available at the time histamine is administered.

Dosage.—For the treatment of Menière's syndrome and multiple sclerosis, a slow, intravenous injection of histamine phosphate, 11 mg per 100 cc, in isotonic sodium chloride solution may be adm

20 to

per

administered in not less than 90 minutes. The therapy may be repeated daily until improvement is noted or until it is determined that the patient will not respond.

Any reaction is to be treated immediately with the intramuscular or intravenous injection of 1:1,000 epinephrine hydrochloride.

DON BAXTER, INC.

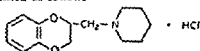
Solution Histamine Phosphate: 250 cc Vacoliter bottles. A solution in isotonic sodium chloride containing 11 mg. of histamine phosphate in each 100 cc.

Agents Used in Differential Diagnosis of Hypertension

Phentolamine is probably even more widely used currently than piperoxan for the diagnosis of pheochromocytoma. It has little pressor action of its own. Tolazoline is used less often and has no advantage over phentolamine. The "attacks" of hypertension may be brought on by administration of histamine or of tetraethylammonium chloride in minute amounts. Dibenamine has no advantage over phentolamine and is more difficult to administer. When the arterial pressure is low, agents such as histamine and tetraethylammonium chloride are the drugs of choice, but for routine screening of patients with essential or malignant hypertension, phentolamine or piperoxan are more useful.

PHENTOLAMINE HYDROCHLORIDE and **PHENTOLAMINE METHANESULFONATE.**—See the monographs in the chapter on autonomic drugs.

PIPEROXAN HYDROCHLORIDE.—Benodaine Hydrochloride (SHARP & DOHME).—2-(1-Piperidylmethyl)-1,4-benzodioxan hydrochloride—The structural formula of piperoxan hydrochloride may be represented as follows



Physical Properties.—Piperoxan hydrochloride is a white, crystalline, odorless powder. It melts between 232 and 236°. It is freely soluble in water, alcohol and chloroform and is very slightly soluble in benzene and ether.

Actions and Uses.—Piperoxan is one of a number of benzodioxan derivatives that exert an inhibiting action on structures innervated by the sympathetic nervous system. The drug usually is designated as adrenolytic rather than sympatholytic, since it reverses the augmentor responses to epinephrine but, except in very large doses, does not depress peripheral sympathetic nervous system responses.

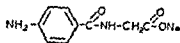
In unanesthetized animals with normal blood pressures, piperoxan may produce a slight rise, moderate fall or no effect on the blood pressure is unaffected or rises slightly. The drug, thus, is oxan produces a temporary fall in blood pressure. Administration of piperoxan to man or animals during an infusion of epinephrine produces a fall in diastolic pressure.

It has been found clinically that patients with epinephrine-producing tumors (pheochromocytomas or paragangliomas) respond to intravenous injection of piperoxan hydrochloride with a transient fall in blood pressure. In other cases of hypertension the blood pressure is unaffected or rises slightly. The drug, thus, is useful in differentiating hypertension due to epinephrine-producing tumors from hypertension due to other causes.

Reported side reactions which sometimes follow intravenous administration of piperoxan hydrochloride include tachycardia, flushing, palpitation, nervousness, cold and clammy extremities, hyperpnea, mild headache, slight sighing respiration, dizziness, substernal pressure and precordial distress. These symptoms occur almost immediately or within 1 or 2 minutes after administration, and rarely last as long as 2 minutes, although in a few instances they have lasted 20 to 25 minutes.

Dosage.—Piperoxan hydrochloride is administered intravenously as a diagnostic test, the recommended dose being 0.25 mg per kilogram of body weight, up to a maximum total dose of 20 mg. No sedative should be given to the patient prior to the test. Isotonic sodium chloride solution is infused slowly into an arm vein of the supine patient. Repeated readings of blood pressure should be made until the pressure is stabilized, usually after 20 to 30 minutes. The last two readings should be made at 1 minute and 1 1/2 minute before administration of piperoxan hydrochloride.

The calculated dose of piperoxan hydrochloride should be administered slowly into the intravenous infusion system over a



Physical Properties.—The pH of the ampul solution of sodium *p*-aminohippurate is not less than 7.0 nor more than 7.6.

Actions and Uses.—Sodium *p*-aminohippurate is filtered by the glomeruli and excreted by the tubular epithelium of the kidneys. It may be used to measure the effective renal plasma flow and to determine the functional capacity of the tubular excretory mechanism. To measure renal plasma flow, low plasma concentrations of sodium *p*-aminohippurate (1 to 2 mg. per 100 cc) are necessary. At these concentrations 88 per cent of this compound is removed by the normal kidney from the renal blood stream in a single circulation. When the excretory capacity of the tubule cells is impaired, renal blood flow as determined by sodium *p*-aminohippurate may be less than that determined directly. The normal effective renal plasma flow is 697 ± 135.9 cc per minute for men and 594 ± 102.4 cc per minute for women. This test cannot be applied to patients receiving sulfonamide compounds, because these develop color with the reagents used in the test.

To determine the functional capacity of the tubular excretory mechanism high plasma concentrations (40 to 60 mg. per 100 cc) of sodium *p*-aminohippurate must be used. The normal mean value of the "tubular excretory mass" is 77.5 ± 12.9 mg. per minute.

Dosage.—To determine effective renal plasma flow, a sterile solution of sodium *p*-aminohippurate is injected intravenously in a volume sufficient to produce approximately 2 mg. of *p*-aminohippurate per 100 cc of blood plasma. At this plasma level all the *p*-aminohippurate in the blood that passes through the normal kidney is removed and appears in the urine. The urine formed during a definite but short period is collected, and the average amount of *p*-aminohippurate eliminated is calculated in milligrams per minute. This value divided by the *p*-aminohippurate content of the plasma in milligrams per cubic centimeter is equivalent to the number of cubic centimeters of plasma per minute that must have passed through the kidneys (effective renal plasma flow).

To determine tubular excretory mass, a sterile solution of sodium *p*-aminohippurate is injected intravenously in a volume sufficient to "saturate" the capacity of the tubular cells to excrete *p*-aminohippurate (40 to 60 mg. per 100 cc of plasma), and the *p*-aminohippurate content of the plasma is determined in milligrams per cubic centimeter. The amount excreted in the urine is determined in milligrams per minute, this value including both glomerular filtration and tubular excretion. The glomerular filtration rate, using mannitol, a compound that is filtered only through the glomeruli, is determined in cubic centimeters per minute (see the monograph on mannitol). From the glomerular filtration rate and the *p*-aminohippurate content per cubic centimeter of plasma is calculated the amount of *p*-aminohippurate that was filtered through the glomeruli in 1 minute (cc/min. \times mg./cc). Then the total number of milligrams excreted in the urine per minute

minus the amount filtered through the glomeruli per minute equals the amount of *p*-aminohippurate in milligrams per minute excreted by the tubules (tubular excretory mass).

SHARP & DOHME, DIVISION OF MERCK & Co, Inc.

Solution Sodium Para-Aminohippurate: 10 and 50 cc. ampuls. A solution containing 0.2 gm. of sodium *p*-aminohippurate in each cubic centimeter.

Water-Insoluble Organic Iodine Compounds for Roentgenography

Water-insoluble organic iodine compounds are administered orally for the radiographic diagnosis of gall bladder disease or injected into such body cavities as the bronchial tree, spinal canal, fallopian tubes and the common bile duct for the radiographic diagnosis of bronchiectasis and pulmonary neoplasm, spinal cord tumors, occlusion of the fallopian tubes and stones in the bile ducts. Various vegetable oils may be used, animal oils cause local irritation. According to the method of iodination, the oil may contain iodine alone, or iodine and chlorine ("chloriodized oils"). These methods do not differ essentially.

Water-insoluble organic iodine compounds are quite viscous. For injections into cavities they may be rendered less viscous by the addition of ethyl oleate, they may be rendered water miscible by emulsification.

As the injection of iodized oils is essentially a surgical procedure, introducing a foreign and possibly irritant body that involves more or less risk, the presumptive advantages should be weighed against the relative advantages and disadvantages of other measures. The following cautions should be especially borne in mind: Oils that have aged and darkened beyond their original color never should be used. Subarachnoid injections should be avoided, at least until all other means of diagnosis have been exhausted. Intratracheal and intrapleural injections should be avoided in tuberculosis of the respiratory organs and also when restriction of respiratory area would be contraindicated. The injection pressure should be controlled carefully, so as not to lacerate the tissues. Intra-uterine injections should be made only under fluoroscopic observations. Iodized oil should not be used for renal pyelography, except in the form of emulsion, and the injection should be stopped if pain is felt. Intravascular injections of halogenated oils involve certain dangers, but several water-soluble compounds have been used widely without serious side effects and with much more satisfactory results.

When the so-called per nasal method of injecting the oil into the larynx is employed, the risk of intoxication from the local anesthetic required for this procedure is enhanced greatly as the absorptive surface is increased.

CHLORIODIZED OIL—Iodochlorol (Stearle)—Chlorinated and iodized peanut oil. A product formed by the chemical addition of

iodine monochloride to peanut oil. It contains 26.5 to 28.5 per cent of iodine in organic combination.

Physical Properties.—Chloriodized oil is a pale yellow, viscous, oily liquid with a faint, bland taste. It is practically insoluble in water, slightly soluble in alcohol and freely soluble in benzene, chloroform and ether.

Actions and Uses.—See the general statement on water-insoluble organic iodine compounds for roentgenography.

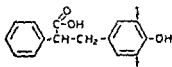
Dosage.—The dose varies with the capacity of the structure to be examined. It ranges from 1 or 2 cc. for small sinuses and fistulas to 20 cc. in the paranasal sinuses and bronchial tract.

G. D. SEARLE & Co.

Iodochlorol: 20 cc. bottles. A halogenated (chloriodized) peanut oil containing about 27 per cent iodine and 7.5 per cent chlorine in organic combination.

U. S. trademark 519,701

IDOALPHIONIC ACID-U.S.P.—**Priodax (SCHERING).**— β -(4-Hydroxy-2,6-diiodophenyl)- α -phenylpropionic acid.—"Iodoalphionic Acid, dried over sulfuric acid for 4 hours, contains an amount of iodine equivalent to not less than 98 per cent and not more than 102 per cent of $C_{15}H_{12}I_2O_3$ " U.S.P. The structural formula of iodoalphionic acid may be represented as follows:



Physical Properties.—Iodoalphionic acid occurs as white crystals or as a white or faintly yellowish powder, having a faint, characteristic odor and taste. It is stable in air but is slightly discolored on prolonged exposure to light. Insoluble in water, it is readily soluble in alcohol and ether and slightly soluble in benzene and chloroform. It is soluble in both alkali carbonate and hydroxide solutions.

Actions and Uses.—Iodoalphionic acid is used as a medium for cholecystography. It causes less nausea, vomiting and diarrhea than tetraiodophenolphthalein. The drug is excreted primarily through the kidneys. See also the general statement on water-insoluble organic iodine compounds for roentgenography.

Although more may be given in cases of water retention. Nothing is contraindicated.

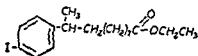
pleted the next morning.

SCHERING CORPORATION

Tablets Priodax: 0.5 Gm.

U. S. patent 2,345,384. U. S. trademark 393,227.

iodophenylundecylate, in uniform, but unknown, proportions. It contains not less than 95 per cent of $C_{19}H_{39}IO_2$ " U.S.P. The principal isomer is thought to be the κ , whose structural formula may be represented as follows:



Physical Properties—Iophendylate is a colorless to pale yellow, odorless, viscous liquid. The color darkens on long exposure to air. It is freely soluble in alcohol, benzene, chloroform and ether and very slightly soluble in water.

Actions and Uses—Iophendylate is an absorbable iodized fatty acid compound of low viscosity designed especially for myelography. It is particularly useful for study of the lumbar region. Intraperitoneal or oral administration in lower animals is moderately toxic, but no toxic phenomena have been observed with massive doses injected intrathecally in higher animals. It is absorbed from the peritoneal cavity of experimental animals in about 6 weeks and from the subarachnoid space of dogs in about 15 months. In humans, intrathecal injection of 2 to 5 cc. is well tolerated even when the agent is left in the spinal canal. When the bulk of the injected material is removed, the remainder usually is absorbed within 2 months. When none is removed, absorption proceeds at a variable rate depending on conditions within the spinal canal, sometimes requiring several years.

The incidence and severity of side effects following myelography with aspiration of iophendylate is only slightly greater than with ordinary lumbar puncture. In 10 to 30 per cent of patients there may be backache and transient elevation in temperature. The agent should not be employed when lumbar puncture is contraindicated, and to avoid subdural and extra-arachnoid extravasation it should not be used within 10 days of a previous lumbar puncture.

Iophendylate also is employed in emulsified aqueous form as a medium for roentgenographic visualization of the biliary tree, sinus and fistulous tracts, ducts and certain body cavities. The emulsion has some advantage over radiopaque oils because of its ability to adhere to mucous membranes, its low viscosity and surface tension and its miscibility with tissue fluids. Since it has not been found satisfactory for bronchography, it is not recommended for that purpose. For cholangiography, it is injected either through a T-tube placed in the common bile duct following surgery or through a catheter inserted into the cystic duct to permit visualization at the time of operation. For visualization of sinuses, fistulas, ducts or cavities, injection is made through a syringe needle or catheter of appropriate size, depending upon the structure to be examined. It is not necessary to remove the emulsion by aspiration or flushing except in enlarged cavities. Retention of the emulsion in

enlarged cavities may interfere with subsequent examinations. The emulsion should not be used intravenously.

Dosage.—For myelography, iophendylate, in undiluted form, is injected intrathecally by lumbar puncture technic; the 2 to 5 cc dose usually is injected between the third and fourth lumbar segments. Care should be exercised to ascertain that the needle point is in the subarachnoid space. The injection should be made slowly to detect unusual resistance from obstruction. The needle with adapter is left in place during myelography to implement removal of the agent when the examination is completed. The agent is removed by aspiration in conjunction with fluoroscopic visualization.

For preoperative and postoperative cholangiography or for visualization of sinus tracts, fistulas, ducts and cavities, a 50 per cent emulsion of iophendylate is injected. In cholangiography, the

ride solution may be required to remove clots, mucus and foreign material prior to injection of the emulsion. It is not necessary to fill large cavities completely, but rotation of the patient may be necessary to reach all surfaces of the structure.

LAFAYETTE PHARMACEUTICAL INC.

Pantopaque: 3 cc ampuls. An undiluted liquid, iophendylate, containing 30.5 per cent iodine in organic combination.

Emulsion Pantopaque 50% V/V: 10 cc ampuls. An emulsion containing 0.5 cc of iophendylate in each cubic centimeter.

U S patent 2,348,231. U S trademark 401,476

Water-Soluble Organic Iodine Compounds for Roentgenography

Unlike the water-insoluble compounds, the water-soluble compounds may be injected into the veins for excretory urography, angiocardiology or cholangiography, or into the arteries for nephrograms or arteriograms. Some of them are suitable also for injection into the ureters for retrograde pyelograms or into the biliary ducts for cholangiography. The compounds also may be used for venograms in the study of varicose veins.

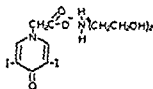
Satisfactory roentgenograms of the urinary tract may be secured by the intravenous injection of nontoxic soluble iodine compounds that are rapidly excreted in the urine. Several organic compounds are now available for this purpose and for ureteral retrograde pyelography. Sodium iodide, in the necessary dose, is too toxic for intravenous injection.

For intravenous urography, no fluids should be given to the patient for several hours (usually from midnight) prior to examination. Restriction of fluids permits greater concentration of the drug. The gastro-intestinal tract should be cleared of gas and re-

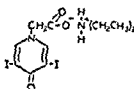
tained materials by enemas and laxatives, preferably with castor oil. If the history of allergy gives any reason to suspect that a reaction may occur, a small initial dose may be given first. In any event, epinephrine hydrochloride 1:1,000 always should be available when the injection is made. The excretory urogram should be made by persons experienced with this method and during the entire procedure the patient should be watched for untoward reactions. Ocular, oral and intradermal tests to detect sensitivity to intravenously administered iodine compounds are not reliable since reactions are more often due to a direct vascular effect. The medium should be given slowly, with a pause after 1 or 2 cc. is injected to note reaction. Care should be exercised to ensure that all the solution is injected into the vein. Some clinicians apply pressure on the bladder region, releasing it immediately before the first exposure and renewing it until the next. Ordinarily, the first film is exposed about 10 minutes after injection and two subsequent pictures are taken at intervals of 15 or 20 minutes. A safe routine is to take roentgenograms 5, 15 and 45 minutes after injection of the drug. When renal function is impaired, the interval is proportionately longer. Side effects that may be encountered include flushing of the face and neck, urticaria, fall in blood pressure, diarrhea, generalized itching and weakness, nausea, vomiting, lacrimation, salivation, edema of the glottis, bouts of coughing, "tight feeling" or choking sensation and cyanosis. These symptoms usually disappear over varying periods of time, but fatalities have occurred.

The intravenous use of these drugs is contraindicated in patients with severe liver disorders, nephritis and severe uremia, and it should be used with caution in cases of active tuberculosis and of hyperthyroidism. Oral use of these compounds is contraindicated in acute disorders of the gastro-intestinal tract. Excretory urography should not be used routinely in all patients. Satisfactory urograms are obtained rarely when the maximum specific gravity of urine is 1.01. Further, this method may have to be checked with retrograde pyelography, and either or both methods closely correlated with the clinical findings. Injection of the medium into the kidney pelvis is gauged most accurately by using a manometer, but in default of this instrument, gravity or a syringe may be employed with care for retrograde pyelography. Because of reflex splanchnic stimulation, anuria has occurred, especially after bilateral examination. Excretory urography or retrograde pyelography may be repeated after an adequate interval.

IODOPYRACET COMPOUND.—*Diodrast Compound* (WINTHROP-STEARNS).—A mixture of the 2,2'-iminodiethanol (commonly called diethanolamine) salt of 3,5-diiodo-4-oxo-1(4H)-pyridineacetic acid and the diethylamine salt of 3,5-diiodo-4-oxo-1(4H)pyridineacetic acid. Iodopyracet compound is prepared by neutralizing 3,5-diiodo-4-oxo-1(4H)-pyridineacetic acid in water with appropriate quantities of diethanolamine and diethylamine. The salts formed are soluble in water and are not isolated. Their structural formulas may be represented as follows:



2,2'-Iminodiethanol salt
of 3,5-diiodo-4-oxo-
1(4H) pyridineacetic
acid



Diethylamine salt of
3,5-diiodo-4-oxo-
1(4H) pyridineacetic
acid

The solution is a clear pale yellow colorless

for roentgenographic visualization of the urinary tract by intra-

Incomplete or absent shadows is the same as when iodopyracet is employed

See also the general statement on water-soluble organic iodine compounds for roentgenography.

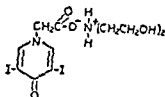
Dosage.—For excretion urography, iodopyracet compound is administered intravenously in sterile aqueous solution, the average dose for adults being 20 cc. Iodopyracet compound in the usual 50 per cent solution may be employed without dilution for retrograde pyelography. For economy, however, more dilute solutions customarily are used. When diluted with 12 cc. of sterile distilled water, a solution of 8 cc. of iodopyracet compound yields 20 cc. of 20 per cent concentration. Dilution of 5 cc. of iodopyracet compound solution with 15 cc. of sterile distilled water (final concentration 12.5 per cent) gives satisfactory pyelograms, this dilution is employed with excellent results in thin people. The volume of fluid generally required for retrograde examination in adults is 20 cc.

WENTHROP-STEARNS, INC.

Compound Solution Diodrest: 20 cc. ampuls.

U. S. trademark 312,431

IODOPYRACET CONCENTRATED.—Diodrest Concentrated (Wentrop-Stearns) — Prepared by neutralizing 3,5-diiodo-4-oxo-1(4H)-pyridineacetic acid in aqueous solution with an excess of diethylamine. The resulting diethylamine salt is isolated and the diethylamine is removed by distillation. The resulting 3,5-diiodo-4-oxo-1(4H)-pyridineacetic acid is then converted to the diethylamine salt. The following is the procedure:



Physical Properties—Iodopyracet concentrated is a stable, colorless or slightly yellowish liquid that may be partially solidified at room temperature. It sometimes forms supersaturated solutions. The pH is between 7.1 and 7.4.

Actions and Uses—Iodopyracet concentrated is employed as a solution in a special diagnostic procedure for visualization of the heart, the ascending and descending aorta and branches, the superior vena cava, the pulmonary artery and branches, the coronary arteries and other structures of the heart and mediastinum. It has been used also for cholangiography by injection of a solution into the common bile duct. The technic in using this agent is complicated and requires accurate timing and teamwork between physician, patient and roentgenologist. The method consists in injecting the substance into the blood and taking roentgenograms simultaneously with the concentration of the opaque material in the cardiopulmonary system. A preliminary x-ray examination of the chest is necessary to obtain data for roentgenography. For accuracy it may be necessary to determine the circulation rate of the blood. Preliminary tests for renal function and sensitivity should be performed. To decrease incidence of nausea and vomiting the stomach should be empty. Premedication with a barbiturate when there is a possibility of a reaction is suggested.

g, sense of intense warmth, sweating, pallor, hypotension, transient pain at the site of injection, headache, fever, chills and cyanosis. Delayed reactions are rare.

Precautions.—This agent should be used only by persons who are experienced.

intravenously only in cases that present difficult diagnostic problems.

Dosage—The amount varies according to the diameter of the chest, the size of existent pulmonary congestion and body weight. For cardiopulmonary visualization 40 to 45 cc. of a solution may be injected intravenously. When visualization of the pulmonary circulation is desired, 30 to 35 cc. may be sufficient. If the intravenous injection must be repeated, 15 minutes should elapse between injections. The duration of injection should be from 1½ to

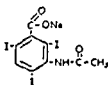
2 seconds. Injection of the material into the tissue outside the vein causes irritation. If crystals are present, warm solution to body temperature before using.

WINTHROP-STEARNs, INC.

Concentrated Solution Diodrast 70% W/V: 20 and 50 cc. ampuls. An aqueous solution containing 70 per cent of the diethanolamine salt of 3,5-diiodo-4-oxo-1(4H)-pyridineacetic acid.

SODIUM ACETRIZOATE.—SODIUM ACETRIZOATE INJECTION—U.S.P.—Urokon Sodium (MALLINCKRODT)—Sodium 3-acetyl-amino-2,4,6-triiodobenzoate—"Sodium Acetrizate Injection is the sterile solution of acetrizic acid in water for injection prepared with the aid of sodium hydroxide. It contains not less than 95 per cent and not more than 105 per cent of the labeled amount of sodium acetrizate ($C_9H_3I_3NNaO_3$)."

"Sodium Acetrizate Injection may contain not more than 0.012 per cent of monocalcium ethylenediamine tetra-acetate as a stabilizer, and not more than 0.015 per cent of sodium biphosphate as a buffer." *U.S.P.* The salt is not isolated from the solution. The structural formula of sodium acetrizate may be represented as follows.



Physical Properties—The solutions are clear and practically colorless. The pH is between 7.0 and 7.4.

Actions and Uses—Sodium acetrizate is employed as a contrast medium for intravenous (excretory) urography, retrograde (transureteral) pyelography, intravenous nephrography and angiocardiology, translumbar arteriography and intraductal cholangiography. It should be used only in these procedures until satisfactory technic has been developed for the visualization of other structures. Although it contains a greater amount of iodine than do other similar agents, studies thus far indicate that it is less toxic.

See also the general statement on water-soluble organic iodine compounds for roentgenography.

Dosage—For intravenous urography, 25 cc. of a 30 per cent solution is considered adequate for adults and children over 4 years of age. Where greater density is desired, 25 cc. of the 70 per cent solution is recommended, and for children under 4 years of age a dose of 500 mg. of sodium acetrizate per kilogram of body weight usually is employed (about 0.7 cc. of sodium acetrizate per kilogram of body weight). In any case, the total time for injection should not be less than 10 seconds and need not be more than 1 minute. Injection should be discontinued immediately in the presence of alarming symptoms. In contrast to the instructions in the general statement on water-soluble organic iodine

compounds, the best results are obtained by making exposures at 5, 10 and 15 minutes after the injection.

For retrograde pyelography the dilute solution employed may contain 30 per cent or less of sodium acetrizoate, depending on the degree of contrast desired. Bilateral ureteral injection usually is

For translumbar arteriography in adults and children 12 years of age or over, 10 to 15 cc. of a 70 per cent solution is sufficient. In children under 12 years of age, a dose proportionate to age is used.

For angiocardiology and nephrography in adults and in children 12 years of age or over, 40 to 50 cc. of a 70 per cent solution is adequate. For children under 12 years of age, a dose proportionate to age is given. For infants and small children, a dose of 1 cc. of the 70 per cent solution per kilogram of body weight is employed.

For intraductal cholangiography, gradual injection through a catheter of 20 to 40 cc. of a 30 per cent solution (5 cc. at a time) usually is adequate for visualization of stones either during or following gallbladder surgery; 10 to 20 cc. of a 70 per cent solution may be used if denser shadows are desired.

MALLINCKRODT CHEMICAL WORKS

Solution Urokon Sodium 30%: 25 cc. ampuls and 25 cc. vials. A solution containing 0.3 Gm. of sodium acetrizoate in each cubic centimeter. Stabilized with 0.05 mg. of calcium ethylenediamine-tetraacetate and buffered with about 0.12 mg. of sodium biphosphate in each cubic centimeter.

Solution Urokon Sodium 70%: 25 cc. ampuls and 50 cc. vials. A solution containing 0.7 Gm. of sodium acetrizoate in each cubic centimeter. Stabilized with 0.12 mg. of calcium ethylenediamine-tetraacetate and buffered with about 0.12 mg. of sodium biphosphate in each cubic centimeter.

U. S. patent 2,611,786, U. S. trademark 519,732.

it may have adjunctive usefulness provided the excretory function of the kidneys is not impaired.

When edema is attributable to hypoalbuminemia, diuresis may be obtained by intravenous injections of normal human serum albumin (salt-poor).

MERCURY COMPOUNDS

The principal mercurial diuretics are similar in structure. They are primarily methoxy-mercuripropyl derivatives of organic acids; frequently the amide derivatives of dibasic acids. Mercumatin differs slightly in that it is a monobasic acid and its mercurated allyl group is attached directly to a carbon atom rather than to a nitrogen atom. The local irritant action of these compounds is diminished and the diuretic efficiency increased by the addition of theophylline or sodium thioglycollate. At present most mercury diuretics are available in combination with theophylline. Acid-producing diuretics, such as ammonium chloride, administered orally prior to injection of the mercurials, increase the diuretic effect of the latter.

Mercurial diuretics are proposed for use in cardiac edema, nephrotic edema, ascites of liver disease and in carefully selected cases of subacute and chronic nephritis complicated by cardiac edema. The diuresis from the mercurials eliminates not only water but also sodium, and thus decreases the body's capacity to retain fluid. In cardiac disease the diuresis may relieve symptoms such as dyspnea even though manifest edema is not present.

Mercurials are contraindicated in acute nephritis and should be used with caution in chronic kidney disease. Since mercury gives rise in sensitive patients to side effects such as stomatitis, gastric disturbances, vertigo, febrile reactions and cutaneous eruptions, initial tests and careful regulation of dosage are suggested when mercury diuretics are used. However, some patient may be sensitive to one mercurial, yet tolerate another satisfactorily. Sudden fatalities have been reported following the use of mercurial diuretics injected intravenously and, although these mishaps are rare, caution should be exercised. Since the evidence indicates that ventricular arrhythmia is the mechanism of these fatalities, special precautions should be taken with patients who already are likely to be affected by such arrhythmia, for example, patients with frequent ventricular extrasystoles, heavily digitalized patients and those with recent myocardial infarction.

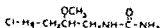
body weight. In the absence of a diuretic response, repeated injections are contraindicated. Especially in cases where sodium chloride is restricted in the diet, prolonged diuresis from repeated injections of mercurials may unduly deplete the body of sodium and cause symptoms of weakness, collapse, hypotension, hemoconcentration

and azotemia. These symptoms can be alleviated promptly by administration of sodium salts. Failure of mercurials to produce diuresis may be due to salt depletion.

Many of these diuretics are effective and relatively safe when administered by intramuscular injection; some may be given subcutaneously.

The mercurial diuretics may be given orally in tablet form. However, oral use can supplant injections in only a very small percentage of cases since this method is much less effective in producing diuresis and may cause symptoms of gastro-intestinal irritation. In some cases the necessity of frequent injection can be diminished by oral medication. These drugs also can be given as rectal suppositories, but the effect produced is mild and the diuresis usually sufficient to control only the milder cases. Rectal irritation sufficient to make other methods of administration preferable occurs fairly frequently.

CHLORMERODRIN—Neohydrin (LAKESIDE)—[3-(Chloromercuri)-2-methoxypropyl]urea.—The structural formula of chlormerodrin may be represented as follows:



Physical Properties—Chlormerodrin is a white, odorless powder with a bitter, metallic taste. It is very soluble in sodium hydroxide T.S. and very slightly soluble in chloroform. The amounts that dissolve in the following solvents to form 100 cc. of solution are: 0.56 Gm. in alcohol, 1.1 Gm. in methyl alcohol and 1.1 Gm. in water. Chlormerodrin is stable to light and air. The pH of a 0.5 per cent solution is 4.3 to 5.0.

Actions and Uses—Chlormerodrin is more effective orally than previously introduced mercurial diuretics that can be administered by this route. Thus, it is useful for oral, mercurial, diuretic therapy in the management of recurring cardiac and nephrotic edema, ascites of liver disease and in carefully selected cases of subacute and chronic nephritis. Chlormerodrin may supplant the need for injection therapy in some patients, but in others parenteral treatment may be required to replace or supplement oral medication.

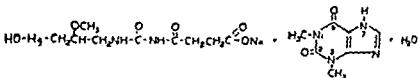
Dosage—Chlormerodrin is administered orally. The average daily dose for adults ranges from 18.3 mg. (equivalent to 10 mg. of mercury) to 71.2 mg. (40 mg. of mercury), depending upon the severity of edema or circulatory failure. The dosage for children is adjusted in proportion to body weight. Reduction of dosage or withdrawal of medication may be necessary to eliminate side effects.

LAKESIDE LABORATORIES, INC.

Tablets Neohydrin. Each tablet contains 18.3 mg. of chlormerodrin (equivalent to 10 mg. of mercury).

U. S. patent 2,433,982. L. S. trademark 543,631.

MERALLURIDE SODIUM.—MERALLURIDE INJECTION.
U.S.P.—Mercuryhydrin Sodium (LAKESIDE).—Sodium 1-(3'-hydroxy-mercuri-2'-methoxypropyl)-3-succinylurea and theophylline—**Meralluride Sodium Injection.**—"Meralluride Injection is a sterile solution of meralluride in water for injection made by the addition of just sufficient sodium hydroxide solution to effect solution of the meralluride. An additional amount of theophylline may be added also. It contains not less than 94 per cent and not more than 106 per cent of the labeled amounts of the mercuri compound ($C_{11}H_{16}HgN_2O_6$) and of theophylline ($C_7H_8N_4O_2 \cdot H_2O$)" *U.S.P.* The structural formula of meralluride sodium may be represented as follows.



Actions and Uses.—Meralluride sodium solution is a mercurial diuretic proposed for use in the edema of cardiorenal disease and of nephrosis, ascites of liver disease and other conditions in which a mercurial diuretic is indicated.

It is well tolerated systemically and, when given intramuscularly, seldom causes pain at the site of injection. It is absorbed rapidly following intramuscular injection. It is administered also by intravenous injection. The drug also is effective when administered by subcutaneous injection, although painful local reactions have been noted in some patients.

For contraindications and cautions, see the general statement on mercury compounds.

Dosage.—Depending on the condition of the patient and route and frequency of administration, the dose of meralluride sodium (in a solution containing 0.13 Gm of meralluride sodium and 10 mg of theophylline per cubic centimeter) varies from 1 to 2 cc. In view of occasional cases of idiosyncrasy to mercurials, the initial dose should be 0.5 cc or less. Subsequent injections may be given twice weekly as indicated by the condition of the patient.

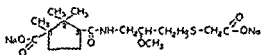
LAKESIDE LABORATORIES, INC

Solution Mercuryhydrin Sodium: 1 and 2 cc ampuls and 10 cc vials. A solution containing 0.13 Gm of meralluride sodium (equivalent to 39 mg of mercury) and 10 mg of excess theophylline in each cubic centimeter. The 10 cc. vials are preserved with 0.13 per cent methylparaben and 0.02 per cent propylparaben.

U. S. patent 2,204,941 U. S. trademark 506,726.

MERCAPTOMERIN SODIUM, STERILE.—U.S.P.—Thiomarin Sodium (Wyeth).—Disodium N-[3-(carboxymethylmercaptomercuri)-2-methoxypropyl]- α -camphoramate—"Sterile Mercaptomerin Sodium, dried in vacuum at 50° for 18 hours, contains not less than 95 per cent and not more than 105 per cent of $C_{16}H_{25}HgNNa_2O_6S$ "

U.S.P. The structural formula of sterile mercaptomerin sodium may be represented as follows.



Physical Properties—Sterile mercaptomerin sodium is a hygroscopic, white solid. It is freely soluble in water, soluble in alcohol, very slightly soluble in ether and practically insoluble in benzene and chloroform.

Actions and Uses—Sterile mercaptomerin sodium is an effective mercurial diuretic that produces much less local irritation on injection than other organomercurial compounds used for this purpose. It is less toxic to the heart than the previously employed mercurial diuretics and shares the other actions of these compounds, including the potential toxic effects of mercury. Preliminary acidification of the urine also sometimes enhances its diuretic effect. See the general statement on mercury compounds.

Sterile mercaptomerin sodium is contraindicated in advanced chronic nephritis and acute renal disease. Care must be taken in its use with drastic sodium chloride restriction to avoid salt depletion from copious diuresis.

Dosage.—Sterile mercaptomerin sodium is administered by subcutaneous injection in the form of a solution, readily prepared from the dry form of the drug, in a concentration of about 0.13 Gm. per cubic centimeter of sterile water (13 per cent). Each cubic centimeter of this solution contains 0.13 Gm. of sterile mercaptomerin sodium, equivalent to 43 mg. of mercury.

Since the drug is highly irritating to the tissues, extreme emaciation may make intramuscular injection preferable.

The dosage of the 13 per cent solution ranges from 0.5 to 2 cc. subcutaneously, depending on the requirements of the individual patient. The drug is sensitive to heat, and should be kept under refrigeration. The solution should be discarded on appearance of turbidity.

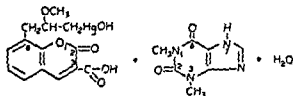
WYETH LABORATORIES, INC.

Powder Thiomerin Sodium, 1.4 and 4.2 Gm. vials. When made up with 10 and 30 cc. of sterile water, respectively, a 13 per cent solution is obtained, each cubic centimeter of which contains 0.13 Gm. of sterile mercaptomerin sodium (equivalent to 43 mg. of mercury).

Suppositories Thiomerin Sodium: 0.5 Gm. of sterile mercaptomerin sodium (equivalent to 0.17 Gm. of mercury).

U. S. trademark 436,086.

MERCUMATILIN.—Cumertilin (ENDO).—8-(2'-Methoxy-3'-hydroxymercuripropyl)coumarin-3-carboxylic acid (mercumallylic acid) and theophylline.—Mercumatilin consists of mercumallylic acid (the mercuri compound $C_{14}H_{14}HgO_6$, mol. wt. 478.86) and of theophylline-U.S.P. in approximately molecular proportions. The structural formula of mercumatilin may be represented as follows:



Actions and Uses.—Mercumatilin is used as a diuretic for the same purposes as other orally effective mercury-theophylline compounds. It should be employed chiefly as an adjunct to parenteral injection of the sodium salt. See the general statement on mercury compounds and the monograph on mercumatilin sodium.

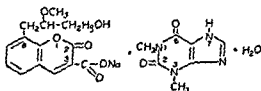
Dosage.—The average daily dose for adults is 67 to 134 mg. Some patients may require 200 to 270 mg daily to reduce the frequency of injections (administered as the sodium salt) needed to maintain an edema-free state.

ENDO PRODUCTS, INC.

Tablets Cumertilin: 67 mg. Each tablet contains 67 mg. of mercumatilin (equivalent to 20 mg. of mercury).

MERCUMATILIN SODIUM.—Cumertilin Sodium (ENDO).—So-

approximately molecular proportions. It is prepared by adding just enough sodium hydroxide solution to mercumatilin to effect solution. The salt is not isolated. An excess over one mole of theophylline may be added. The structural formula of mercumatilin sodium may be represented as follows:



Actions and Uses.—Mercumatilin sodium produces the same diuretic effect as other mercury-theophylline compounds, from

which it differs slightly only in chemical structure. Its injection causes local irritation similar to that produced by the other organic mercurial diuretics which are suitable only for intramuscular or intravenous injection. See also general statement on mercury compounds

recommended is 2 cc intramuscularly, or 1 to 2 cc. intravenously, at biweekly intervals. Shorter or longer intervals may be used in accordance with the degree of edema or dehydration present. Injections should be made at different sites to avoid undue local irritation. Mercumatilin sodium should be employed with the same precautions as other mercurial diuretics.

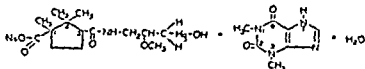
ENDO PRODUCTS, INC.

Solution Cumertilin Sodium: 1 and 2 cc. ampuls and 10 cc. vials. An aqueous solution containing 0.132 Gm. of mercumatilin sodium (equivalent to 39 mg. of mercury) and 11 mg. of excess theophylline in each cubic centimeter. The 10 cc. vials are preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

Solution Cumertilin Sodium with Benzyl Alcohol 2%: 10 cc. vials. An aqueous solution containing 0.132 Gm. of mercumatilin sodium (equivalent to 39 mg. of mercury) and 11 mg. of excess theophylline in each cubic centimeter.

MERCUROPHYLLINE SODIUM.—MERCUROPHYLLINE-U.S.P.
—*Mercuzanthin* (CAMPBELL).—"Mercurophylline consists of the

contains not less than 94 per cent and not more than 106 per cent of the labeled amount of the mercuri compound and of anhydrous theophylline ($C_7H_8N_4O_2$). "U.S.P. The structural formula of mercurophylline may be represented as follows.



Physical Properties.—Mercurophylline sodium occurs as a white or slightly yellow, odorless powder. It is moderately hygroscopic and slowly darkens on exposure to light. Its solutions are alkaline to litmus paper. One gram of mercurophylline sodium dissolves in about 5 cc. of water. It is soluble in alcohol, but insoluble in ether and in mineral oils.

Actions and Uses.—Mercurophylline sodium is a potent diuretic.

It is less toxic and more active than the purine-free mercurial diuretics. When theophylline is combined with the mercurial, sloughs and venous thromboses occur with less frequency and severity. The presence of theophylline enhances the rate and completeness of absorption, so that the drug is effective and well tolerated by intramuscular as well as intravenous administration.

Diuresis develops slowly following oral administration of mercuriophylline and does not reach its peak for 48 hours. The total diuretic response may approach that produced by intravenous injection. Reactions to orally administered mercuriophylline include gastro-intestinal irritation and possible kidney damage after prolonged use.

Dosage.—Solutions of mercuriophylline containing 0.135 Gm. to 0.155 Gm. per cubic centimeter, stabilized with an excess of theophylline, are employed for intramuscular injection. Benzyl alcohol occasionally is added to lessen the pain of intramuscular injection. To discover intolerance to the preparation, a much smaller trial dose should be injected. Caution must be exercised to prevent leakage into the subcutaneous tissue.

Intravenous injection may be carried out with similar concentrations of the drug, but more dilute concentrations not containing benzyl alcohol are preferred, since unpleasant side effects may occur with the concentrated solution.

When maximum diuresis is desired in patients with massive edema, approximately 275 mg. administered at one time will usually produce a response comparable to that obtained with repeated injections. In severe cases, reaccumulation of the dropsical fluid may be partly or entirely controlled with 60 to 110 mg. daily; in milder cases with occult edema, 60 to 110 mg., three times daily on 2 or 3 successive days is recommended. Oral dosage for maintenance is 100 to 200 mg. daily.

CAMPBELL PHARMACEUTICAL COMPANY

Enteric Coated Tablets Mercuzanthin (Sodium): 0.1 Gm. (equivalent to 28 mg. of mercury).

Solution Mercuzanthin (Sodium): 1 and 2 cc. ampuls. A solution containing 0.135 Gm. of mercuriophylline sodium (equivalent to 38 mg. of mercury) in each cubic centimeter.

U. S. patent 2,117,901. U. S. trademark 418,334.

FLINT, EATON & COMPANY

Solution Mercuriophylline (Sodium): 1 and 2 cc. ampuls. A solution containing 0.15 Gm. of mercuriophylline sodium (equivalent to 43 mg. of mercury) in each cubic centimeter.

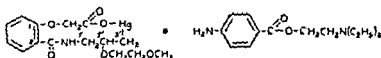
LINCOLN LABORATORIES, INC.

Solution Mercuriophylline (Sodium): 1 and 2 cc. ampuls. A solution containing 0.14 Gm. of mercuriophylline sodium (equivalent to 39 mg. of mercury) in each cubic centimeter.

PRIMO PHARMACEUTICAL LABORATORIES, INC.

Solution Mercurophylline (Sodium).—2 cc ampuls. A solution containing 0.14 Gm of mercurophylline sodium (equivalent to 39 mg of mercury) in each cubic centimeter.

MERETHOXYLLINE PROCAINE.—Dicurin Procaine (Lilly).—Dehydro-2-[N-(3'-hydroxymercuri-2'-methoxyethoxy)propylcarbamyl]phenoxycetic acid (merethoxylline), 2-diethylaminoethyl p-aminobenzoate (procaine) and theophylline.—Merethoxylline procaine consists of a mixture of 1 mol of the procaine salt of merethoxylline (the mercuri compound, $C_{17}H_{19}HgNO_6$, mol wt 509.92) and 1.4 mols of anhydrous theophylline-U.S.P. It is prepared by dissolving merethoxylline and procaine in water and then adding the theophylline. It is not isolated from solution. The structural formulas of the compounds may be represented as follows:



Merethoxylline Procaine



Theophylline (Anhydrous)

Action and Uses.—Merethoxylline procaine has the same actions and uses as other mercurial diuretics. See the general statement on mercury compounds. It is used to prevent or control excessive accumulation of fluid in the tissue spaces and body cavities as an adjunct in the management of congestive heart failure, cirrhosis of the liver with ascites and nephrosis.

The toxicity of merethoxylline procaine is no greater than that of other organic mercurial compounds. The procaine component minimizes the discomfort of local irritation that may be produced by the mercurial compound when injected into the tissue. In such reactions are not encountered frequently. Like similar mercurial diuretics, it should not be administered in the presence of sensitivity to mercury or theophylline, acute glomerulonephritis, ulcerative colitis or gouty diathesis. Sensitivity to procaine is a contraindication, and, because of that component, physicians should be alert for possible signs of such a reaction in susceptible patients. As with any diuretic, it should be used with caution in benign prostatic hypertrophy when duration of the treatment exceeds 60 mg. per 100 cc. If a transient increase in blood urea nitrogen after administration of the drug is noted, it is common.

Dosage.—Merethoxylline procaine is administered intravenously.

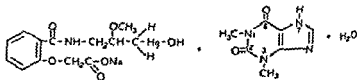
larly or subcutaneously. Intravenous administration is not advised, because diuretic effectiveness is seldom greater and the risk of deleterious side effects is increased greatly. Subcutaneous injection should be deep because superficial deposit of the drug predisposes the patient to local reaction. The drug is injected as an aqueous solution containing 0.195 Gm. of the salt per cubic centimeter. This includes 0.1 Gm. of the organic mercurial component (equivalent to 39.3 mg. of mercury), 0.05 Gm. of theophylline, and 0.043 Gm. of procaine base. The initial dose should be 0.5 cc. of such solution to preclude a serious reaction resulting from idiosyncrasy. In adults, the average subsequent daily dosage is a single injection of 2 cc. preferably in the morning, or this can be administered as two injections of 1 cc. each. Alternative sites of injection should be used to reduce the possibility of local reactions.

ELI LILLY & COMPANY

Solution Dicurin Procaine. 2 cc. ampuls and 10 cc. vials. A solution containing 0.1 Gm. of merethoxylline as the procaine salt (equivalent to 39.3 mg. of mercury) and 50 mg. of theophylline in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

MERSALYL SODIUM AND THEOPHYLLINE.—MERSALYL AND THEOPHYLLINE INJECTION (AND TABLETS)—U.S.P.—Mersalyn (KIRK)—Salyrgan-Theophylline (WINTHROP-STEARNS)—Sodium *o*-(3-hydroxymercuri-2-methoxypropyl)carbamylphenoxacetate and theophylline—"Mersalyl and Theophylline Injection is a sterile solution in water for injection of approximately 2 parts by weight of mersalyl ($C_{13}H_{16}HgNNaO_6$) to 1 part by weight of theophylline ($C_7H_8N_4O_2 \cdot H_2O$). It contains not less than 94 per cent and not more than 106 per cent of the labeled amount of mersalyl ($C_{13}H_{16}HgNNaO_6$) and of theophylline ($C_7H_8N_4O_2 \cdot H_2O$).

"Mersalyl and Theophylline Tablets contain not less than 90 per cent and not more than 110 per cent of the labeled amount of mersalyl ($C_{13}H_{16}HgNNaO_6$) and of theophylline ($C_7H_8N_4O_2 \cdot H_2O$)." U.S.P. The structural formulas of mersalyl sodium and of theophylline may be represented as follows:



Physical Properties.—Mersalyl sodium and theophylline each occur as a white or almost white, crystalline powder. They are odorless and have a bitter taste. Theophylline is stable in air. Mersalyl sodium is somewhat deliquescent and is decomposed gradually by light; its solutions are alkaline to litmus paper. One gram of mersalyl sodium dissolves in about 1 cc. of water, 1 Gm. of theophylline dissolves in about 120 cc. of water.

Actions and Uses—Mersalyl sodium and theophylline has been demonstrated to produce less local reaction on intramuscular or intravenous injection than mersalyl sodium alone and to be more effective. The more rapid resorption of mersalyl sodium in combination with theophylline accelerates diuresis and, by preventing the deposition of mercury, improves the local tolerance. Mersalyl sodium and theophylline is proposed as a diuretic for dropsy in cardiac edema and in nephrosis and ascites of liver diseases. It is contraindicated in acute nephritis and chronic kidney disease without edema and in intestinal inflammation with diarrhea. For side effects and cautions, see general statement on mercury compounds.

Dosage—The adult dose of 0.2 Gm. of mersalyl sodium and 0.1 Gm. of theophylline may be injected intramuscularly or intravenously. For susceptibility, test the patient with one-half of the recommended dose. If the test dose is well tolerated, the recommended dose may be given on the following day. In some cases this dose may have to be doubled for the full effect. Injections usually are not given more frequently than every 3 or 4 days. After relief of the dropsy, recurrences often can be prevented by occasional injections. One dose of about 0.3 Gm. may be given in the morning after breakfast and repeated in 4 to 5 days if required. As an adjunct to parenteral medication, about 0.1 Gm. may be given orally every day for 1 or 2 weeks, but in such instances rest periods of 1 or 2 weeks should intervene between courses of treatment. For children the dosage should be reduced by one-half.

C. F. KERR COMPANY

Solution Mersalyn with Benzyl Alcohol 2%: 2 cc ampuls and 10 and 30 cc vials. A solution containing 0.1 Gm. of mersalyl sodium (equivalent to 40 mg. of mercury) and 30 mg. of theophylline in each cubic centimeter.

S. E. MASSENGILL COMPANY

Solution Mersalyl (Sodium) and Theophylline. 2 cc ampuls. A solution containing 0.1 Gm. mersalyl sodium (equivalent to 39.6 mg. mercury) and 30 mg. of theophylline in each cubic centimeter.

WINTHROP-STEARNS, INC.

Solution Salyrgan (Sodium) Theophylline. 1 and 2 cc ampuls and 1 cc. Ampuls. A solution containing 0.1 Gm. mersalyl sodium (equivalent to 40 mg. of mercury) and 30 mg. theophylline in each cubic centimeter.

Enteric Coated Tablets Salyrgan (Sodium) Theophylline. Each tablet contains 80 mg. mersalyl sodium (equivalent to 32 mg. of mercury) and 40 mg. theophylline.

U. S. Patent 2,213,437 U. S. trademark 183,513

XANTHINE DERIVATIVES

Caffeine, theobromine and theophylline are methylxanthines, derived from xanthine by the introduction of two or three methyl

radicals at the corresponding number of heterocyclic nitrogen atoms. As these may occupy various positions in the xanthine nucleus, a number of methylxanthines exist, naturally and by synthesis, differing quantitatively in pharmacologic activity. Those named, however, are the only ones of therapeutic importance; caffeine is 1,3,7-trimethyl-

s 3,7-dimethyl-
The structural



Caffeine usually is obtained from tea or coffee; theobromine is obtained from cacao or is made synthetically. Theophylline occurs in nature but in amounts too small to be commercially available, so it is prepared synthetically.

Theobromine and theophylline surpass caffeine in their diuretic and perhaps in cardiac and muscular actions. Therefore, they are generally preferred in cardiac edemas, etc., since they are equally or more effective, more prompt and largely avoid the unpleasant side effects of caffeine.

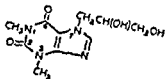
Probably not so lasting, it may produce gastric disturbances or renal irritation. If central stimulation is desired, caffeine should be used. In recent years, diuresis by administration of the xanthine derivatives in combination with the more effective mercurial diuretics has superseded the use of the methylxanthine alone.

usefulness. Therefore, they are used almost exclusively in the form of the readily soluble double salts, which they form with a number of compounds: theobromine and sodium salicylate, theobromine and sodium acetate, theophylline and sodium acetate and aminophylline (theophylline ethylenediamine). Because of its greater solubility (1 Gm. in 5 cc. of water) aminophylline is used most commonly. While it is not a particularly potent or reliable diuretic, it is useful as a peripheral vasodilator and has a more pronounced stimulant action on the myocardium than the other xanthines. It is useful by intramuscular or intravenous injection in the treatment of pulmonary edema, the paroxysmal dyspnea of congestive heart failure and paroxysms of bronchial asthma or status asthmaticus, particularly when this condition is refractory to epinephrine. From 0.25 to 0.5 Gm. may be given slowly intravenously; rapid injection may result in undue fall in blood pressure or vomiting. Aminophylline also is sometimes effective by inhalation as an aerosol in the control of dyspnea of cardiac or asthmatic origin.

There is no reason to suppose that the particular salt used to procure the solubility has any material influence on the action. The dosage of these added compounds also is generally too small to produce therapeutic effects. Therefore, it may be assumed that the various preparations are equivalent. There is no basis for claims that the xanthines effectively control arterial hypertension. Increased coronary blood flow which follows rather than precedes myocardial stimulation cannot be considered an adequate basis to support claims for use of the drug in coronary disease or angina pectoris.

Theophylline Compounds

HYPHYLLINE.—Neophylline (PAUL MANEY) —7-(2,3-Dihydroxypropyl)theophylline.—The structural formula of hyphylline may be represented as follows



Physical Properties.—Hyphylline is a white, almost odorless, extremely bitter, amorphous solid, with a melting point between 155 and 160°. It is freely soluble in water and practically insoluble in ether. The approximate amounts that dissolve at 25° in the following solvents to form 100 cc of solution are 2 Gm in alcohol and 1 Gm in chloroform. The pH of a 1 per cent solution is between 6.5 and 7.0.

Actions and Uses.—Hyphylline, a neutral derivative of theophylline, is stable in gastric juice. Although hyphylline can be administered orally in more effective doses than most theophylline compounds (such as aminophylline), it has not been shown to be superior in this respect to theophylline-sodium glycinate. It exhibits the characteristic peripheral vasodilator and bronchodilator actions of other theophylline compounds and, in contrast to those that are poorly tolerated by the stomach, it can be expected to be effective orally in the treatment of bronchial asthma, paroxysmal cardiac dyspnea and Cheyne-Stokes respiration. Hyphylline also produces the typical diuretic and myocardial stimulant effects of theophylline compounds, which are useful in the management of edema secondary to congestive heart failure. Its use in coronary disease or angina pectoris is not recommended until it can be demonstrated that increased coronary blood flow precedes rather than follows myocardial stimulation.

The toxicity of hyphylline in mice is considerably less than that of aminophylline; this difference has not been demonstrated in man, except that it tends to produce less nausea, clinically, when given orally because it produces less gastric irritation than other theophylline compounds. Large doses of hyphylline, like those of

other xanthines, may be associated with unpleasant symptoms of central nervous system stimulation.

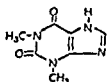
Dosage.—Hyphylline is administered orally; for adults, an average dosage is 0.2 Gm. three times daily. Smaller oral doses may be adequate to produce muscle in congestive heart failure for the control of bronchospasm and Cheyne-Stokes respiration in accordance with the clinical use of the drug. When oral theophylline compounds such as

PAUL MANEY LABORATORIES, INC.

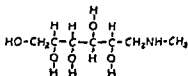
Tablets Neothylline: 0.1 and 0.2 Gm.

U. S. trademark 574,923.

THEOPHYLLINE-METHYLGLUCAMINE.—Glucophylline (Abbott).—An equimolecular mixture of theophylline-U.S.P. ($C_7H_8N_4O_2 \cdot H_2O$) and N-methylglucosamine ($C_7H_{17}NO_5$). Dosage forms of theophylline-methylglucamine contain not less than 95 per cent nor more than 105 per cent of the labeled quantities of theophylline and methylglucamine. The structural formula of theophylline and of methylglucamine may be represented as follows:



Theophylline



Methylglucamine

Actions and Uses.—Theophylline-methylglucamine is identical in action and therapeutic purpose to aminophylline (theophylline ethylenediamine) over which it has no advantage. Therefore, it is similarly useful orally and by injection to produce the effects of theophylline when a more soluble salt than theophylline and sodium acetate is needed. It is administered as a peripheral vasodilator and myocardial stimulant for pulmonary edema and paroxysmal dyspnea in congestive heart failure, and for the relief of Cheyne-Stokes respiration. It is useful also in the relief of acute bronchial asthma, particularly in patients who have become unresponsive to epinephrine. As with aminophylline, claims for its use in coronary or peripheral vascular disease and in hypertension are not confirmed by available evidence.

Dosage.—Theophylline-methylglucamine represents about 50 per cent of theophylline, as compared to about 78 per cent contained in aminophylline, so that the ratio of dosage to the latter is approximately 2:3. The dosage recommended for theophylline—one-half times the

—times daily after

meal-, given for only a few days at a time with intervening rest periods of 1 or 2 days. The intramuscular dosage is 0.75 Gm in 2 cc, the intravenous dosage, 0.36 to 0.75 Gm in 10 to 20 cc. As with aminophylline, intravenous injection should be made slowly to avoid untoward effects.

ABBOTT LABORATORIES

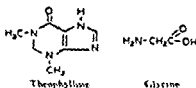
Solution Glucophylline. 2 cc ampuls. A solution containing 0.36 Gm of theophylline-methylglucamine in each cubic centimeter.

Suppositories Glucophylline (Rectal): 0.5 Gm

Tablets Glucophylline: 0.15 and 0.3 Gm

U. S. patent 2,161,114 U. S. trademark 334,367

THEOPHYLLINE SODIUM GLYCINATE-N.F.—Cinaphyl (ASCHER)—Dorsaphyllin (SMITH-DORSEY)—Glynazan (FIRST TEXAS CHEMICAL)—Glytheonate (PATHE)—Synophyllate (CENTRAL)—Theoglycinato (BRAYEN)—“Theophylline Sodium Glycinate is an equilibrium mixture containing theophylline sodium ($C_7H_7N_4NaO_2$) and glycine ($C_2H_5NO_2$) in approximately molecular proportions buffered with an additional mole of glycine. Dried at 105° for 4 hours, it contains not less than 49 per cent and not more than 52 per cent of theophylline ($C_7H_8N_4O_2 \cdot H_2O$).” N.F. The structural formula of theophylline and of sodium glycinate may be represented as follows:



Physical Properties.—Theophylline sodium glycinate is a white, odorless powder with the characteristic bitter taste of theophylline. It decomposes between 190 and 210° . It is freely soluble in water and is decomposed by acids.

Actions and Uses.—Theophylline sodium glycinate has the typical action of solubilized forms of theophylline such as theophylline sodium acetate and aminophylline (theophylline ethylenediamine), with the advantage that it is more stable in air and less irritating to the gastric mucosa. Thus, it is tolerated in larger oral doses than are possible with other theophylline preparations, and it can be administered by mouth in liquid form as well as in tablets not enteric coated. It is incompatible with acidic drugs. Theophylline sodium glycinate is only slightly less soluble than aminophylline and is also suitable for intravenous injection. It can be administered alone or alternated with penicillin as an aerosol for inhalation in the treatment of severe bronchial asthma. Until more evidence becomes available theophylline sodium glycinate should be used only for the purposes recognized for aminophylline. Its value in cardiac con-

ditions other than paroxysmal cardiac dyspnea is not established

Dosage.—Theophylline sodium glycinate consists of approximately 50 per cent of anhydrous theophylline, whereas aminophylline consists of approximately 80 per cent. The dose of theophylline sodium glycinate thus should be about one-third more than that of aminophylline

The oral dose of powder, tablets, elixir or syrup, given every 4 to 6 hours. Adults, 0.3 to 1 Gm.; children over 12 years, 0.15 to 0.4 Gm.; children, 6 to 12 years, 0.1 to 0.2 Gm.; children, 3 to 6 years, 0.13 Gm.; children 1 to 3 years, 0.065 to 0.13 Gm. The powder or tablets are administered preferably with water after meals. Until rectal doses for children are established, suppositories are recommended only for adults. The adult rectal dose is 0.78 Gm. every 4 to 6 hours

The initial intravenous dose in emergencies is 0.4 Gm. in 10 cc of water for injection-U.S.P., administered slowly to test its effectiveness and the tolerance of the patient. When necessary, twice this amount (0.8 Gm. in 20 cc) may be administered slowly and repeated three to four times daily until oral therapy can be instituted or resumed

Theophylline sodium glycinate may be administered as an aerosol by nebulization with oxygen of a 5 to 10 per cent solution for inhalation, preferably under a canopy. Nebulization of 2 cc. of such a solution every 4 hours may be effective in refractory cases of bronchial asthma; very severe dyspnea may require continuous therapy or alternate inhalation of nebulized anti-infective agents such as penicillin.

B. F. ASCHER & COMPANY, INC.

Tablets Cinaphyl: 0.33 Gm

BRAYTEN PHARMACEUTICAL COMPANY

Powder Theoglycinate: Bulk; 113 Gm. bottles, for compounding U.S.C.

Suppositories Theoglycinate: 0.78 Gm.

Syrup Theoglycinate: 240 cc bottles. A syrup containing 32 mg. of theophylline sodium glycinate in each cubic centimeter.

Tablets Theoglycinate: 0.325 Gm

U. S. trademark 501,300

THE CENTRAL PHARMACAL COMPANY

Powder Synophylate: 113 Gm.

Solution Synophylate: 10 and 20 cc. ampuls. A solution containing 40 mg. of theophylline sodium glycinate in each cubic centimeter.

Suppositories Synophylate: 0.78 Gm.

Syrup Synophylate: 480 cc. and 3.84 liter bottles. A syrup con-

taining 82 mg of theophylline sodium glycinate in each cubic centimeter.

Tablets Synophylate: 0.16 and 0.33 Gm.

FIRST TEXAS CHEMICAL MANUFACTURING COMPANY

Elixir Glynazan: 473 cc. and 3.78 liter bottles. An elixir containing 70 mg of theophylline sodium glycinate in each cubic centimeter.

Powder Glynazan, 113 and 454 Gm. bottles

Syrup Glynazan: 473 cc. and 3.78 liter bottles. A syrup containing 35 mg of theophylline sodium glycinate in each cubic centimeter.

Tablets Glynazan, 0.324 and 0.162 Gm

THE E. L. PATCH COMPANY

Powder Glytheonate: 113 and 454 Gm. bottles.

Suppositories Glytheonate: 0.78 Gm

Syrup Glytheonate: 473 cc. and 3.78 liter bottles. A syrup containing 65 mg of theophylline sodium glycinate in each cubic centimeter

Tablets Glytheonate: 0.324 Gm.

U. S. trademark 507,062

SMITH-DORSEY, DIVISION OF THE WANDER COMPANY

Suppositories Dorsaphyllin: 0.78 Gm

Elixir Dorsaphyllin: 473 cc. and 3.78 liter bottles. An elixir containing 42.5 mg of theophylline sodium glycinate in each cubic centimeter

Tablets Dorsaphyllin 0.32 Gm

U. S. trademark 556,322

Enzymes

The enzymes presently accepted for inclusion in *New and Non-official Remedies* have been grouped together in this chapter in the belief that the increasing use of this class of agents will necessitate separate classification.

HYALURONIDASE.—HYALURONIDASE FOR INJECTION.—U.S.P.—Alidase (SEARLE).—Enzodase (SQUIBB).—Hyazyme (ABBOTT)—Wydase (WYETH).—"Hyaluronidase for Injection is a sterile, dry, soluble enzyme product prepared from mammalian testes and capable of hydrolyzing mucopolysaccharides of the type of hyaluronic acid. Its potency, in U.S.P. Hyaluronidase Units, is not less than the labeled potency. Hyaluronidase for Injection contains not more than 0.25 microgram of tyrosine for each U.S.P. Hyaluronidase Unit. It may contain a suitable stabilizer." U.S.P.

Physical Properties.—Hyaluronidase for injection is a white, amorphous solid. Its solutions are colorless and odorless.

Actions and Uses.—The activity of hyaluronidase usually is determined either by measuring the reduction in turbidity that it produces when it acts on a substrate containing native hyaluronate and certain proteins, or by measuring the reduction in viscosity that it produces on a buffered solution of sodium or potassium hyaluronate. At present, each manufacturer defines his product in terms of turbidity-reducing units or viscosity units, depending on the system of standardization used. These units are not equivalent since they are measures of different properties of the enzyme.

Hyaluronic acid, an essential component of the "ground substance" of tissues, limits the spread of fluids and other extracellular material. Since hyaluronidase softens tissue hyaluronic acid, the enzyme causes injected solutions or local accumulations of fluids (transudates and blood) to spread further and faster than normal and facilitates their absorption.

Hyaluronidase may be used to increase the spread and, consequently, the absorption of hypodermoclysis solutions; to diffuse local anesthetics at the site of injection, particularly in nerve block anesthesia, to increase the diffusion and absorption of other injected materials such as penicillin; and to increase the diffusion and absorption of local accumulations of transudates or blood.

Hyaluronidase also enhances local anesthesia in surgery of the eye. It is useful when administered as a cone injection in glaucoma, since it causes a temporary drop in intra-ocular pressure.

Hyaluronidase is practically nontoxic, but caution must be used in administering it to patients with infections. The enzyme may cause local infections to spread through the same mechanism by

which the spread of injected solutions is facilitated. *Until further evidence is available, hyaluronidase should not be injected into or about an infected area*

Sensitivity to hyaluronidase occurs infrequently. It can be discovered by testing the skin in the usual manner

Dosage.—Hyaluronidase is supplied in a stable, dried form for the preparation of extemporaneous solutions and as a solution containing a stabilizing agent to protect the enzyme against deterioration when it stands in solution over long periods of time.

each 1,000 cc of hypodermoclysis fluid or injected at the site to be employed immediately prior to instituting the clysis. Special care is advisable in pediatric patients to control the speed and total volume of fluid administered to avoid over-hydration, in children less than 3 years of age the volume of a single clysis should be limited to 200 cc, in premature infants and during the neonatal period, the daily dosage should not exceed a volume of 25 cc per kilogram of body weight, the rate of administration should not exceed 2 cc per minute. In adults the rate and volume of administration should not exceed that employed for intravenous infusion.

The agent also is used for addition to drug preparations or to small amounts of anesthetic solutions for subcutaneous injection. For nerve block or infiltration requiring larger amounts of anesthetic solution, 150 turbidity-reducing units or 500 viscosity units and 0.5 cc of epinephrine hydrochloride 1:1,000 are added to each 50 cc of solution and injected intracutaneously, subcutaneously or intramuscularly.

For local anesthesia of the eye, 150 turbidity-reducing units or 500 viscosity units are dissolved in 1 cc of a 2 per cent procaine hydrochloride solution (or equivalent amount of other anesthetic to be used) and 0.4 per cent potassium sulfate. For nerve block, 0.4 cc of this mixture is diluted to 10 cc, and 0.12 cc (two drops) of epinephrine hydrochloride 1:1,000 is added prior to injection. For cone injection, twice as much epinephrine may be used.

ABBOTT LABORATORIES

Hysryme: Vials containing 150 turbidity-reducing units of sterile lyophilized hyaluronidase

U. S. trademark 364,837

G. D. SEARLE & Co.

Alidase (Dried): Ampuls containing 500 viscosity units of powdered hyaluronidase and 9 mg. of sodium chloride

U. S. trademark 370,583

E. R. SQUIBB & SONS, DIVISION OF OLIV MATTHEWSON CHEMICAL CORPORATION

Enzodase Lyophilized: Vials containing 150 or 1,500 turbidity-

enzyme a-
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methods.

Actions and Uses.—Streptokinase and streptodornase are proteolytic extracellular enzymes produced by cultural growth of hemolytic streptococci (Lancefield's Group C, human strain H46A). These enzymes are employed together in solution as a purified bacteria-free filtrate that has been frozen and dried. The filtrate is purified and this purification may effect a reduction in the relative amounts of other enzymes produced during the fermentation, such as hyaluronidase and ribonuclease. It also may contain certain enzyme-inhibiting substances whose action is minimized by appropriate dilution. The active enzymes function best in a slightly alkaline solution, thus the filtrate is buffered to maintain a pH of ± 7.5 .

In addition to their proteolytic activity, streptokinase and streptodornase stimulate two types of nonspecific reaction, a local outpouring of fluid and phagocytes at the site of application and, in certain instances, a foreign protein type of pyrogenic reaction that is attributed to the absorption of cleavage products produced by the enzymes. The latter reaction occurs usually only when the enzymes are injected into a closed space, especially when this is limited and drainage is delayed.

Streptokinase and streptodornase are used to remove clotted blood or fibrinous or purulent accumulations present following trauma or inflammation, thereby facilitating the action of anti-infective forces (humoral and antibiotic) and encouraging normal repair of tissues. The enzymes are established clinically for use as an adjunct in the treatment of hemothorax, hematoma, empyema and chronic suppurations involving draining sinuses, osteomyelitis, infected wounds or ulcers and other common suppurative lesions. As an adjunct to surgical intervention in the care of chronic suppurations, the enzymes may aid in making secondary closure more effective. They should be employed as supplements rather than as substitutes for surgical debridement and drainage. They also may be of value as an aid in the prevention of post-operative adhesions. The enzymes do not act upon fibrous tissues, mucoproteins or collagen, thus, whenever an area of hemorrhage or pyogenic exudate is in a state of organization, their action is less efficacious. They are of no value in the treatment of inflammations unless suppuration is present.

Streptokinase and streptodornase should not be employed in the presence of active hemorrhage or acute cellulitis without suppuration, because they may interfere with clotting or encourage the spread of nonlocalized infections. When bronchopleural fistulas have been present there is danger of reopening, especially with active tuberculosis. With other types of fistulas, the enzymes may be used with proper precautions.

Streptokinase and streptodornase must not be administered intravenously.

Dosage.—Streptokinase and streptodornase are applied by injec-

tion into cavities and topically by means of wet dressings or added to other materials suitable for keeping the enzymes in close contact with the substrate. The enzymes are used as a solution containing 100,000 Christensen units of streptokinase and at least 25,000 units of streptodornase in not less than 10 cc. of isotonic sodium chloride solution. For a hemothorax or thoracic empyema an initial dose of 200,000 units of streptokinase and 50,000 units of streptodornase is recommended for injection into one or more sites, as indicated. The most effective final concentration ranges from 100 to 500 units per cubic centimeter of the fluid *in situ*. For treatment of tuberculous empyema the special procedures reported in the literature should be followed carefully. For exudates within small, enclosed spaces, the size and concentration of the dose should be related to the size of the cavity. In general, this should provide for the increased volume that results from the liquefying action of the enzymes. For example, a suitable initial dose in maxillary sinus empyema would be 10,000 to 15,000 units of streptokinase and 2,500 to 3,750 units of streptodornase in 2 to 3 cc. of solution. For enzymatic debridement, similar concentrations may be applied by means of suitable dressings (this is still under investigation to determine optimal methods). Adequate provision should be made for complete drainage of the liquefied exudate. In a fixed rigid space the dosage interval for repeated injections will range from 30 minutes to 6 hours, depending on the size of the space, in empyemas of the chest, 12 to 24 hours usually is suitable. The amount and character of the fluid aspirated or drained serve as a guide to the number of applications required. This must be evaluated to determine whether the drainage results from increased inflammatory activity or from unresolved exudate requiring further enzyme treatment. Streptokinase usually produces a demonstrable effect within 1 hour and streptodornase somewhat sooner. Maximal liquefaction usually is obtained within 12 to 24 hours. The action of the enzymes is self-limiting, within 24 to 48 hours, because of the interference of serum inhibitors and because a state of equilibrium is reached between substrates and end products. In addition, the action of streptokinase is limited by the amount of human serum factor present. Since both enzymes are antigenic and stimulate production of antienzymes, these may reduce activity after 2 to 3 weeks unless larger amounts are employed to offset such inhibition. Appropriate precautions are necessary to avoid allergic reaction in sensitive patients.

Solutions deteriorate in potency at room temperatures and may be held for 7 days at 2 to 10° (35.6 to 50° F.). Strict aseptic precautions are essential to avoid contamination.

LESTER LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

Powder Vardase 24 cc. vial. A sterile powder containing the equivalent of 100,000 units of streptokinase and 25,000 units of streptodornase. Buffered with sodium phosphates to a pH of 7.5. Preserved with thimerosal 1:10,000.

Gastro-intestinal Agents

The class of drugs affecting the motor and secretory activities of the gastro-intestinal tract is very large. The present chapter includes only antacids, cholagogues, emollients and laxatives. Certain other drugs that affect the secretions and movements of the gastro-intestinal tract will be found in the chapter on autonomic drugs.

ANTACIDS

The purpose of antacid therapy is to neutralize effectively the continuously secreted acid gastric juice. Effective neutralization generally is regarded as achieving a pH of 4.0 or 5.0; at this hydrogen ion concentration, the hydrochloric acid and, simultaneously, the peptic activity are practically eliminated. Antacids act locally upon the gastric content; since they do not inhibit the activity of the acid secreting cells, their effects are temporary and disappear when the medication is discontinued.

Aluminum hydroxide is less effective than calcium carbonate in neutralizing gastric acidity in patients with

ALUMINUM HYDROXIDE

—Al-U-Creme

(WINTUROF-S)

cially as Alur

Hydroxide Ge

Aluminum Hydroxide Gel is a suspension containing an equivalent of not less than 36 per cent and not more than 44 per cent of aluminum oxide (Al_2O_3), in the form of aluminum hydroxide and hydrated oxide. It may contain peppermint oil, glycerin, sorbitol, sucrose, saccharin, or other suitable agents for flavoring purposes, and it may contain sodium benzoate, benzoic acid, or other suitable agents, in a total amount not exceeding 0.5 per cent, as a preservative.

"Dried Aluminum Hydroxide Gel yields not less than 50 per cent of aluminum oxide (Al_2O_3)" U.S.P.

Physical Properties.—Aluminum hydroxide gel is a white, viscous suspension, translucent in thin layers, from which small amounts of water may separate on standing.

Actions and Uses.—Aluminum hydroxide is an effective gastric antacid neutralizing hydrochloric acid of the stomach by chemical reaction. It has none of the principal disadvantages of soluble basic salts. It does not increase the pH of the gastric juice to the point of interference with peptic digestion, does not stimulate a compensatory increase in free gastric acidity and does not produce systemic alkalization. The amphoteric nature of alumi-

num hydroxide is not of clinical significance because it reacts as an acid only in fluids with a pH above 9; such a pH is not encountered in the gastro-intestinal tract. Its so-called buffer action occurs only at a pH of about 4. It is presumed that the acid salt aluminum chloride, which is formed by the reaction of aluminum hydroxide with hydrochloric acid in the stomach, is reconverted to the original compound or other aluminum compounds by reaction with the less acid contents of the small intestine, and that the chloride is reabsorbed.

Its mild astringent and demulcent properties are believed to be of some importance in the local effect on peptic ulcer. Its effectiveness may be explained further by the tendency to increase mucin secretion. This action has not been demonstrated *in vivo*.

Like other aluminum compounds, aluminum hydroxide is not absorbed from the gastro-intestinal tract to any appreciable extent and, therefore, is nontoxic when administered orally. Because of its astringency, it may cause constipation.

Administration of excessive amounts of aluminum compounds may interfere with the absorption of certain minerals and can produce a phosphorus deficiency. This does not result from ordinary doses employed in indigestion, peptic ulcer and gastric hyperacidity, and the diet employed in these conditions ordinarily is rich in phosphorus. Aluminum hydroxide may possess adsorptive properties, but specific conclusive evidence that acids, toxins, bacteria or gases are adsorbed is lacking. Its reaction with hydrochloric acid is accounted for completely on the basis of simple chemical neutralization.

Aluminum hydroxide is recognized for oral use as an adjunct in the treatment of peptic ulcer (gastric and duodenal) to promote healing, relieve pain and control hemorrhage and for the control of gastric hyperacidity. Its oral or rectal use in the treatment of other gastro-intestinal conditions is not supported adequately by clinical evidence.

Dosage.—Aluminum hydroxide is administered orally as aluminum hydroxide gel USP in doses of 4 to 8 cc in one-half glass of water or milk every 2 or 4 hours, or $\frac{1}{2}$ to 1 hour after meals. It may be administered by continuous drip by stomach tube in dilutions of 1 part to 2 or 3 parts of water (25 to 33½ per cent aluminum hydroxide gel) at the rate of 15 to 20 drops a minute for a total of approximately 1,500 cc of diluted suspension per 24 hours.

Tablets of dried aluminum hydroxide gel-USP may be used when it is difficult or inconvenient for the patient to take the liquid form.

LANE Medical Laboratories, Inc.

Tablets Alligel 032 and 063 Grs

U. S. trademark 111,663

MACALLISTER LABORATORY

Al-U-Creme 450 cc and 386 liter bottles. A suspension containing 55 per cent aluminum hydroxide (equivalent to 36 per cent

aluminum oxide) with saccharin sodium and peppermint oil as flavoring agents.

PAUL MANEY LABORATORIES

Gel Aluminum Hydroxide: 480 cc. bottles. A suspension containing the equivalent of 3.6 to 4.4 per cent of aluminum oxide.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Dried Aluminum Hydroxide Gel: 0.3 and 0.65 Gm.

THE RESERVE RESEARCH COMPANY

Gel Aluminum Hydroxide: 360 cc. bottles. A suspension containing 5.5 per cent of aluminum hydroxide (equivalent to 3.6 per cent of aluminum oxide) and peppermint oil, orange and vanilla as flavoring agents.

Gel Aluminum Hydroxide (Unflavored): 360 cc. bottles. A suspension containing 5.5 per cent of aluminum hydroxide (equivalent to 3.6 per cent of aluminum oxide).

WILLIAM H. RORER, INC.

Gel Aluminum Hydroxide: 355 cc. and 3.79 liter bottles. A suspension containing the equivalent of 3.6 to 4.4 per cent of aluminum oxide.

Tablets Dried Aluminum Hydroxide Gel (Flavored): 0.3 Gm.

THE UPJOHN COMPANY

Gel Aluminum Hydroxide: 237 cc. and 3.78 liter bottles. A suspension containing the equivalent of 3.6 to 4.4 per cent of aluminum oxide.

THE VALE CHEMICAL COMPANY, INC.

Tablets Dried Aluminum Hydroxide Gel: 0.324 Gm.

VELTEX COMPANY

Gel Aluminum Hydroxide: 480 cc. and 3.84 liter bottles. A suspension containing the equivalent of 3.95 to 4.3 per cent of aluminum oxide with saccharin and peppermint oil as flavoring agents and sodium benzoate as a preservative.

THE VITARINE COMPANY, INC.

Gel Aluminum Hydroxide: 236.5 and 473 cc. and 3.78 liter containers. A suspension containing aluminum hydroxide equivalent to 4 per cent of aluminum oxide, with soluble saccharin and peppermint oil as flavoring agents and preserved with sodium benzoate.

WINTHROP-STEARNs, INC.

Creamalin: 240 and 480 cc. bottles. A suspension containing 5.5 per cent aluminum hydroxide (equivalent to 3.6 per cent aluminum oxide). Peppermint oil is added as a flavoring agent.

WYETH LABORATORIES, INC.

Suspension Amphojel (Flavored): 180 and 360 cc. bottles. A suspension containing the equivalent of 3.6 to 4.4 per cent aluminum oxide, 2.5 per cent glycerin and not more than 0.5 per cent sodium benzoate. Flavored with peppermint oil.

Suspension Amphojel (Unflavored): 180 and 360 cc. bottles. A suspension containing the equivalent of 3.6 to 4.4 per cent aluminum oxide, 2.5 per cent glycerin and not more than 0.5 per cent sodium benzoate.

Tablets Amphojel: 0.3 and 0.6 Gm.

U. S. trademark 370,518.

ALUMINUM PHOSPHATE PREPARATIONS.—Phosphaljel (WYETH)—Aluminum phosphate is available commercially as Aluminum Phosphate Gel-U.S.P.—“Aluminum Phosphate Gel is a water suspension containing not less than 3.8 per cent and not more than 4.5 per cent of aluminum phosphate (AlPO_4). It may contain peppermint oil, glycerin, sorbitol, sucrose, saccharin, or other suitable agents for flavoring purposes, and it may contain sodium benzoate, benzoic acid, or other suitable agents, in an amount not exceeding 0.5 per cent, as a preservative” U.S.P.

Physical Properties.—Aluminum phosphate gel is a white, viscous suspension from which small amounts of water may separate on standing. The pH of aluminum phosphate gel at 25° is between 6.0 and 7.2.

Actions and Uses.—Aluminum phosphate has antacid, astringent and demulcent properties analogous to those of aluminum hydroxide but does not interfere with phosphate absorption. Because the acid-combining power of aluminum phosphate is less than one-half that of aluminum hydroxide of the same concentration, it is necessary to prescribe amounts more than twice as great. Indications for the selection of aluminum phosphate include ulcers if a high phosphate diet cannot be continuously maintained or if they are accompanied by a deficiency of pancreatic juice or by diarrhea. Aluminum phosphate gives as good results as aluminum hydroxide in the treatment of peptic ulcers when it is employed in sufficient amounts.

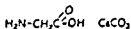
Dosage.—During the active stage of the ulcer, 15 to 30 cc. of the suspension, aluminum phosphate gel-U.S.P. alone or with water or milk may be administered every 2 hours. Later the dose may be reduced to 45 cc. four times daily (with or after each meal and at bedtime) or to 30 cc. six times daily (with or after and between meals and at bedtime).

WYETH LABORATORIES, INC.

Phosphaljel: 360 cc. bottles. A suspension containing 4 per cent of aluminum phosphate, 1.5 per cent of glycerin, not more than 0.5 per cent of sodium benzoate as a preservative and peppermint oil as a flavoring agent.

U. S. patent 2,294,319 U. S. trademark 337,611.

AMINOACETIC ACID AND CALCIUM CARBONATE.—*Titralac* (SCHENLEY).—Glycine and calcium carbonate.—A mixture containing 30 per cent of aminoacetic acid-N.F. and 70 per cent of calcium carbonate-U.S.P. The formulas of these compounds may be represented as follows:



Physical Properties.—Aminoacetic acid and calcium carbonate is a white, odorless, crystalline powder having a slightly sweetish taste. The aminoacetic acid is soluble in water; the calcium carbonate is insoluble.

Actions and Uses.—Aminoacetic acid and calcium carbonate, in the above proportions, produce an acid neutralization curve simu-

systemic alkalosis frequently attributed to the use of alkalis alone. It may be particularly suited for use as a source of calcium in patients unable to take milk, but its buffering action is in no way superior to that which might be achieved with a diet rich in milk and cream. The only claim recognized for the effect of aminoacetic acid is that it has acid buffering action in the mixture.

Dosage.—Aminoacetic acid and calcium carbonate is administered orally in doses containing 0.15 Gm. of aminoacetic acid and 0.35 Gm. of calcium carbonate. It may be taken with milk. For peptic ulcer, one or two doses are taken at hourly intervals until symptoms are brought under control.

SCHENLEY LABORATORIES, INC.

Liquid Titralac: 236 cc. bottles. A suspension containing 60 mg. of aminoacetic acid and 0.14 Gm. of calcium carbonate in each cubic centimeter.

Tablets Titralac: Each tablet contains 0.15 Gm. of aminoacetic acid and 0.35 Gm. of calcium carbonate.

U. S. patent 2,429,596.

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and carbonates.

Physical Properties.—Basic aluminum carbonate as a suspension is a white, creamy, thixotropic gel which may separate to some extent on standing. On exposure to atmospheric pressure, the preparation gradually loses carbon dioxide, it must be kept in tightly closed containers. The pH of basic aluminum carbonate suspension is between 6.6 and 7.0.

Actions and Uses.—Like aluminum hydroxide, but unlike aluminum phosphate, basic aluminum carbonate combines with the phosphate ion in the intestinal tract to form insoluble aluminum phosphate which is excreted as such in the stool. This diminishes the amount of phosphate available for intestinal resorption, which temporarily lowers the serum inorganic phosphorus and favors more complete tubular resorption by the kidney, thus reducing urinary excretion of phosphate. Basic aluminum carbonate is about one-third more effective than aluminum hydroxide in phosphorus-binding power, this is attributed partly to its greater aluminum content. Therefore, basic aluminum carbonate is primarily useful, in conjunction with a low phosphorus diet, to reduce the concentration and precipitation of urinary phosphate in patients susceptible to the formation of phosphatic calculi of the urinary tract. Thus, it may be used as an adjunct in the prevention or management of phosphatic stone formation in the kidneys, ureters and bladder. Limitation of phosphorus intake and diversion of phosphate through the intestine by means of basic aluminum carbonate is proposed to replace the use of urine acidifiers and the acid-ash diet for control of the urinary precipitation of phosphate when the latter method is ineffectual because of the presence of ammonia-forming bacterial infection or could lead to acidosis resulting from impairment of renal function.

Basic aluminum carbonate shares the antacid properties of other aluminum compounds used to control gastric hyperacidity and as an adjunct in the treatment of peptic ulcer. Its acid-consuming capacity is greater than that of the upper allowable range of an equivalent weight of aluminum hydroxide.

Basic aluminum carbonate is not contraindicated in the presence of kidney damage or in the presence of an alkaline urine caused by persistent infection. It shares the tendency to produce constipation secondary to the mild astringent action that is characteristic of similar aluminum preparations, but usually this can be controlled easily by the concomitant administration of a mild laxative.

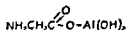
Dosage.—Basic aluminum carbonate is administered orally. In the management of phosphatic urinary calculi, the dosage should be regulated according to the urinary phosphorus excretion of the patient. The average initial adult dose is 10 cc four times daily, preferably taken after meals and at bedtime. In the majority of patients, this will reduce urinary phosphate excretion within a few days to 0.7 Gm or less per 24 hours. The urinary phosphate should be determined at least once a month, and the patient should be placed on a diet designed to provide a daily mineral intake of 1.5 Gm of phosphorus, 0.7 Gm of calcium and 11 Gm of nitrogen, and to furnish about 2,500 calories. Such a diet can be followed for an indefinite period by the average ambulant patient.

The average antacid dose for adults is 4 to 8 cc., repeated as necessary to control gastric hyperacidity.

WYETH LABORATORIES, INC.

Suspension Basaljel: 360 cc. bottles. A flavored aqueous suspension containing the equivalent of 4.9 to 5.3 per cent of aluminum oxide and not less than 2.4 per cent of carbon dioxide.

DIHYDROXYALUMINUM AMINOACETATE-N.F.—Alglyn (BRAYTEN).—Aspogen (EATON)—Alzinox (PATCH).—Dimothyn (FLINT, EATON).—Doraxamin (SMITH-DORSEY).—Robalate (ROBINS).—Basic Aluminum Glycinate—"Dihydroxyaluminum Aminoacetate, dried to constant weight at 130°, contains not less than 92.5 per cent and not more than 107.5 per cent of $C_2H_5AlNO_4$." N.F. The structural formula of dihydroxyaluminum aminoacetate may be represented as follows.



Physical Properties.—Dihydroxyaluminum aminoacetate is a white, odorless powder with a faintly sweet taste. It is insoluble in water and organic solvents, but dissolves in dilute mineral acids and solutions of fixed alkalis to yield cloudy solutions which clarify on heating.

Actions and Uses.—Dihydroxyaluminum aminoacetate acts as a gastric antacid when taken orally and, thus, is useful for the control of hyperacidity in the management of peptic ulcer. It shares the properties of the aluminum hydroxide gel preparations. In vitro studies indicate that the buffering action of dihydroxyaluminum aminoacetate in tablet form is comparable to that of the liquid preparations of aluminum hydroxide gel when compared on the basis of equivalent aluminum content. The clinical significance of differences between dihydroxyaluminum aminoacetate and preparations of aluminum hydroxide is open to question, and claims that it is generally superior to aluminum hydroxide preparations are disallowed until conclusive clinical evidence is available.

Dosage.—Dihydroxyaluminum aminoacetate is administered orally 0.5 to 1 Gm. after meals and at bedtime or as otherwise required to control hyperacidity. As with other internally administered aluminum compounds, constipation may occur from prolonged administration.

BRAYTEN PHARMACEUTICAL COMPANY

Tablets Alglyn: 0.5 Gm

U. S. patent 2,480,743 U. S. trademark 420,509.

EATON LABORATORIES

Tablets Aspogen: 0.5 Gm.

U. S. trademark 505,100

FLINT, EATON & COMPANY

Tablets Dimothyn: 0.5 Gm.

THE E. L. PATCH COMPANY

Magma Alzinox: 250 cc bottles. A suspension containing 0.1 Gm of dihydroxyaluminum aminoacetate in each cubic centimeter. Preserved with 0.1 per cent of sodium benzoate.

U. S. patent 2,480,743

Tablets Alzinox: 0.5 Gm.

A. H. ROBINS COMPANY, INC.

Tablets Robalato: 0.5 Gm.

U. S. trademark 344,956

SMITH-DORSEY, DIVISION OF THE WANDER COMPANY

Gel Doraxamin: 473 cc bottles. A gel containing 0.1 Gm of dihydroxyaluminum aminoacetate in each cubic centimeter. Preserved with 0.015 per cent of butyl *p*-hydroxybenzoate.

Tablets Doraxamin: 0.5 Gm.

U. S. trademark 562,594

ALMAGUCIN.—Mucotin (HARROWER).—An antacid mixture of gastric mucin, dried aluminum hydroxide gel-U.S.P. ($\text{Al}_2\text{O}_3 \cdot x\text{H}_2\text{O}$), and magnesium trisilicate-U.S.P. ($2\text{MgO} \cdot 3\text{SiO}_2 \cdot x\text{H}_2\text{O}$), containing the labeled amounts of these ingredients.

Actions and Uses.—This mixture of histamine-free gastric mucin, aluminum hydroxide and magnesium trisilicate is an effective combination for oral administration in the control of symptomatic gastric hyperacidity and as an adjunct in the treatment of peptic ulcer. Gastroscopic studies indicate that the mucin-antacid combination may coat the ulcer crater and may remain in the stomach for over an hour after instillation. However, the coating effect ascribed to this preparation requires further confirmation, if it occurs, its therapeutic value remains to be established. Antacid effect is secured by the aluminum hydroxide and magnesium trisilicate.

Dosage.—There is as yet no definite evidence by which to determine the optimum proportions of the antacids to be used in the mixture, but best results are obtained with preparations containing approximately 10 per cent of gastric mucin. A ratio of 1:1.5:2.75 for gastric mucin:aluminum hydroxide:magnesium trisilicate produces good results. A tablet preparation of these proportions, containing 0.16 Gm gastric mucin, 0.25 Gm dried aluminum hydroxide gel and 0.45 Gm magnesium trisilicate, is recommended in doses of two tablets every 2 hours. The tablets should be well chewed and no fluids taken during the following half hour.

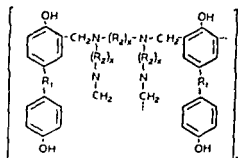
HARROWER LABORATORY, INC.

Liquid Mucotin: 355 cc bottles. A flavored suspension containing 40 mg of gastric mucin, 62 mg of aluminum hydroxide gel and 0.11 Gm of magnesium trisilicate in each cubic centimeter.

Tablets Mucotin: Each tablet contains gastric mucin 0.16 Gm., dried aluminum hydroxide gel 0.25 Gm. and magnesium trisilicate 0.45 Gm. with excipients and flavoring oils.

U. S. patent 2,472,476, applied for, Lutheran Univ. Assoc., Valparaiso University. U. S. trademark 519,949.

POLYAMINE-METHYLENE RESIN.—Exorbin (ALERST).—Resinat (NATIONAL DRUG)—A polyethylene polyamine methylene substituted resin of diphenylol dimethylmethane and formaldehyde in basic form. The structural formula of polyamine-methylene resin may be represented as follows:



Physical Properties.—Polyamine-methylene resin is a light amber, granular, freely flowing powder without appreciable odor. It is insoluble in dilute acids and alkalis, alcohol, ether and water; however, a small amount of colored material is extracted by aqueous systems.

Actions and Uses.—Polyamine-methylene resin is a synthetic acid-binding resin capable of withdrawing acids from solution by molecular absorption. This property has been utilized clinically by administering the resin orally as a gastric antacid for the control of symptoms in simple hyperacidity and in peptic ulcer. The antacid effects apparently result from temporary binding in the stomach of gastric hydrochloric acid and pepsin which are later released in the intestine. The resin itself then is eliminated unchanged from the gastro-intestinal tract without any permanent ionic disturbance of the body fluids. Like other antacids, this resin should be regarded as only an adjunct in the treatment of peptic ulcer; it is not recommended in the treatment of gastritis, "heartburn" or dyspepsia, which may or may not be associated with increased gastric acidity. Recommendations for its use in simple gastric hyperacidity should not imply that it is of value in all diseases in which this condition exists, unless it can be demonstrated that the symptoms are directly related to the hyperchlorhydria.

Polyamine-methylene resin is essentially nontoxic, but large doses may induce nausea or vomiting unless the taste of the resin is masked suitably.

Dosage.—Polyamine-methylene resin is administered orally in the form of powder, capsules or tablets. For the relief of symptoms in acute or chronic peptic ulcer, 0.5 to 1 Gm. every 2

should be stirred quickly in water, milk or other liquid, but it is probably more palatable in the form of capsules or tablets

AYERST LABORATORIES, INC.

Tablets Exorbin: 0.25 Gm.

U. S. trademark 530,289.

NATIONAL DRUG COMPANY

Capsules Resinat: 0.25 Gm

Tablets Resinat: 0.5 Gm.

U. S. patent 2,581,035 U. S. trademark 519,752

EMOLLIENTS

Substances possessing an adhering and protective quality are used in the treatment of peptic ulcer. Usually they are prescribed in mixtures with other agents, such as antacids.

GASTRIC MUCIN.—The fraction precipitated by approximately 60 per cent alcohol from the supernatant liquid after pepsin-

viscous gray, opalescent solution when triturated with water

Actions and Uses.—Gastric mucin is used in the treatment of peptic ulcer. Its therapeutic action is considered to be that of protecting and lubricating the mucosa of the stomach and duodenum. Currently available preparations of gastric mucin do not effectively neutralize gastric acidity in man.

Dosage.—The average dose is 2.5 Gm., which can be given at 2-hour intervals.

WILSON LABORATORIES

Granules Gastric Mucin: 226.8 and 453.6 Gm. packages.

Powder Gastric Mucin: 453.6 Gm. packages.

LAXATIVES AND CATHARTICS

Laxatives and cathartics are compounds that facilitate the passage and elimination of feces from the colon and rectum. They are of three general types: irritants, bulk-producers and emollients.

Irritant laxatives increase the propulsive peristaltic activity of the colon by irritating the mucosa or by directly stimulating the smooth muscle of the bowel. Cascara and senna contain anthracene

derivatives; the active principle is absorbed partially and excreted in the urine and in the milk of lactating women. *Cascara sagrada*, obtained from *Rhamnus persiana*, acts only upon the large intestine; therapeutic doses produce soft fecal evacuations within 6 to 24 hours. Prolonged ingestion of cascara frequently results in a characteristic, melanotic pigmentation of the rectal mucosa, easily noted d

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considerable abdominal cramping distress. Rhubarb, another member of this group, also contains the astringent, tannin. Aloin is the active principle of aloes; hydrolysis of this glycoside yields an anthraquinone that is quite irritating, causing severe abdominal cramps and pelvic vascular congestion; large quantities of aloes reportedly are injurious to the kidneys. Cathartics such as Jalap powder depend for their action upon the hydrolysis of resinous glycosides; the resultant acids stimulate peristaltic activity of the small intestine and decrease antiperistalsis in the colon; these compounds are too violent and should not be prescribed. Castor oil, obtained from the seed of *Ricinus communis*, contains the triglyceride of the unsaturated hydroxy fatty acid, ricinoleic acid. The digestion of castor oil liberates the highly irritating ricinoleic acid, directly stimulating peristaltic activity of the small bowel. The intestinal contents are propelled so rapidly through the colon that they prevent the normal absorption of fluid; a therapeutic dose of castor oil usually causes liquid stools within a few hours. Croton oil is the most powerful and dangerous of all cathartics and should never be used. Phenolphthalein is insoluble in water and passes unchanged through the stomach into the small intestine where it dissolves in the alkaline contents. Phenolphthalein, an ingredient of many proprietary laxatives, irritates the small bowel mildly and stimulates the musculature of the colon vigorously; therapeutic doses induce defecation within 8 or 10 hours; severe enteric distress, sunken skin, ether and hemorrhagic tendencies

small bowel, producing liquid fecal evacuations, usually within several hours after oral ingestion. Magnesium sulfate, because of vescent action as a Magnesium oxide red form to overcome the constipating action of calcium carbonate in ulcer therapy. Small amounts of the magnesium ion are absorbed but are excreted too rapidly to cause toxic effects if renal function is normal.

Hydrophilic colloid laxatives absorb water from the bowel con-

tents, the increased bulk stimulating peristaltic activity and modifying the consistency of the feces. These compounds, however, do not interfere with the absorption of nutrients.

ever, fecal impaction,

been reported. Agar,

marine algae, contains:

seeds are obtained from

or *P. ovata*; the whole gums were formerly taken, without chewing, mixed with fruit juices, but now preparations containing only the extracted gums are available and have the advantage of being less irritating mechanically. Methylcellulose, a synthetic material prepared by treating cellulose with methylchloride, is a relatively inert hydrophilic colloid, adsorbing water to a quantity 10-fold its original weight.

Emollient laxatives lubricate the intestinal tract, preventing excessive fecal dehydration and, thereby, facilitating elimination of the feces. Liquid petrolatum is an indigestible mixture of liquid hydrocarbons extensively used in the management of constipation; taken at mealtimes, it may coat the particles of food, interfering with digestion and absorption. Petrolatum also may hinder the absorption of fat-soluble carotene and vitamins A, D and E.

Evacuant enemas increase peristaltic activity of the large intestine by means of -

tion of irritants, s

these effects Olive

may be prescribed

and lubricate the feces. Evacuant suppositories containing soap or glycerin induce defecation by sensory irritation of the anus; they are effective only when fecal material is present in the rectal ampulla.

Laxatives and cathartics are prescribed and self-administered much more often than is necessary. In many instances constipation is a manifestation of the irritable bowel syndrome, responding to adequate dietary management, mild sedatives and antispasmodics and to the re-establishment of normal bowel habits. Laxatives and cathartics do not relieve chronic constipation permanently. Indeed, their excessive use causes increased irritability of the bowel and disrupts normal reflex activity of the colon.

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10. *Chlorophyll *a** and *Chlorophyll *b** were determined by the method of Lichtenthal and Whistler (1973).

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LETTER COUNCIL OFFICER: David A. Gibson, General

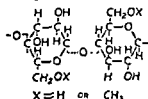
METHYLCELLULOSE-U.S.P. — Cellothyl (WARNER-CHILCOTT) —

Syncolose (BLUX LING)—"Methylcellulose is a methyl ether of cellulose containing not less than 36 per cent and not more than

cellulose containing not less than 20 per cent and not more than

METHYLCELLULOSE-U.S.P.—Cellothyl (WARNER-CHILCOTT)—Synalosa (BLUX LUXE)—“Methylcellulose is a methyl ether of cellulose containing not less than 26 per cent and not more than

33 per cent of methoxy (OCH_3) groups, calculated on the dried basis. The viscosity of a solution containing 2 Gm of Methylcellulose in each 100 ml. is not less than 80 per cent and not more than 120 per cent of that stated on the label for viscosity types of 100 centipoises or less; and not less than 75 per cent and not more than 140 per cent of that stated on the label for viscosity types higher than 100 centipoises." *U.S.P.* The structural formula of methylcellulose may be represented as follows:



Physical Properties.—Methylcellulose is a grayish white, fibrous powder; its aqueous suspensions are neutral to litmus paper. It swells in water and produces a clear to opalescent, viscous, colloidal solution. It is insoluble in alcohol, in ether and in chloroform.

Actions and Uses.—Methylcellulose is used in chronic constipation. This state usually results from a combination of nervous tension, improper dietary and fluid intake, failure to heed the call to stool, lack of exercise and the abuse of laxatives. Hence the administration of drugs should be only an adjunct to re-educative measures.

Taken with water, the drug forms a colloidal solution in the upper alimentary tract; this solution loses water in the colon to produce a gel which increases the bulk and softness of the stool. In the course of a few days the patient may be able to resume more normal bowel habits, and the initial dose should be reduced to a level adequate for maintenance of good function. The drug is customarily continued for weeks or months, usually at reduced dosage. The gelatinous nature of the colonic contents, which results from the use of methylcellulose, may be helpful in patients with colostomies.

Dosage.—For adults, 1 to 1.5 Gm in the form of tablets or granules, with water, two to four times daily; later 1.5 Gm. once or twice daily may be sufficient.

For infants and children, 0.5 Gm as granules, sprinkled on food or stirred in water, two to three times daily.

THE BLUE LINE CHEMICAL COMPANY

Tablets Syncelose; 0.5 Gm.

WARNER-CHILCOTT LABORATORIES, DIVISION OF WARNER-HUDNUT, INC.

Granules Cellothyl; 25 and 100 Gm bottles.

Tablets Cellothyl; 0.5 Gm.

U. S. trademark 428,768.

PLANTAGO OVATA COATING.—Konsyl (BURTON, PARSONS).—A preparation consisting principally of the separated outer mucilaginous layers of *Plantago ovata* seeds (blond psyllium)

Physical Properties.—*Plantago ovata* coating is a cream-colored to brown, granular powder, which is practically odorless and tasteless.

Actions and Uses.—*Plantago ovata* coating may be used in cases of simple constipation due to lack of sufficient bulk in the stool. It produces no cathartic action and is, therefore, mainly useful as an aid in chronic constipation of functional or nervous origin.

Dosage.—5 to 10 Gm. three times daily, usually before meals, in a glass of water or milk, is sufficient to promote evacuation of the bowel in most cases. It is important that the mixture be taken before it thickens.

BURTON, PARSONS & COMPANY

Powder Konsyl: 180 and 360 Gm. cans.

U S patent 1,975,731 U S. trademark 313,620.

PSYLLIUM HYDROPHILIC MUCILLOID WITH DEXTROSE.—

Metamucil (SEARLE).—A mixture containing about 50 per cent of the powdered mucilaginous portion (outer epidermis) of blond psyllium seeds (*Plantago ovata*-Forsk) and about 50 per cent of powdered anhydrous dextrose, with 0.2 per cent sodium bicarbonate, 0.25 per cent monobasic potassium phosphate, 0.33 per cent

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or

formed when 10 Gm. of the powder is stirred rapidly into 250 cc of water. As the hydration and swelling of the mucilaginous portion progresses, the mixture assumes a soft gelatinous consistency.

Actions and Uses.—Psyllium hydrophilic mucilloid with dextrose is intended as an adjunct in the treatment of constipation. It encourages elimination by the formation of a soft, plastic, water-

visualization

Dosage.—Four to 8 Gm. one to three times daily, each time after

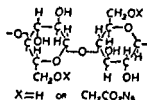
must be ingested to assure a soft bulk. Psyllium hydrophilic mucilloid with dextrose should not be used carelessly as dependency may ensue.

G. D. SEARLE & Co

Metamucil: 113, 227 and 454 Gm. containers.

U S patent 2,095,259 and 2,132,484 U S trademark 317,704

SODIUM CARBOXYMETHYLCELLULOSE-U.S.P.—Thylose Sodium (JACKSON-MITCHELL).—"Sodium Carboxymethylcellulose is the sodium salt of a polycarboxymethyl ether of cellulose. It contains not less than 6.98 per cent and not more than 8.50 per cent of sodium (Na), calculated on the dried basis." *U.S.P.* The structural formula of sodium carboxymethylcellulose may be represented as follows:



Physical Properties.—Sodium carboxymethylcellulose is a white to light buff, odorless, hygroscopic powder. On heating, it browns between 226 and 228° and chars between 252 and 253°. A 1 per cent solution has a pH between 6.5 and 8.0.

it is insoluble in gastric juices. It is a satisfactory and desirable adjunct to re-education in the treatment of chronic constipation.

Dosage.—The usual dose is 1.5 Gm. three times daily with meals, accompanied by one or two glasses of water.

THE EVRON COMPANY, INC.

Tablets Sodium Carboxymethylcellulose: 0.5 Gm.

VICTOR M. HERMELIN AND COMPANY, NEW PRODUCTS DIVISION OF KEITH-VICTOR PHARMACAL COMPANY

Tablets Sodium Carboxymethylcellulose: 0.5 Gm.

JACKSON-MITCHELL PHARMACEUTICALS, INC.

Tablets Thylose Sodium: 0.5 Gm.

Hormones and Synthetic Substitutes

This chapter includes substances that are secreted internally by particular organs whence they are carried by blood or lymph to other organs for the control of growth or activity. Such substances are called endocrine secretions or hormones. Included here also are a number of artificial substances that are important in therapeutics because their actions so closely resemble those of the natural substances.

ADRENALS

Adrenal Cortex

The cortex of the adrenal gland is essential for life. Adrenal-

Adrenal Cortical Extracts.—Extracts of the adrenal cortex contain several potent substances that influence electrolyte, water or carbohydrate metabolism to various degrees. These substances tend to regulate the number of circulating eosinophils and the activity of thymus and lymphoid tissue. They also exert influence over skin pigmentation in human beings. However, as demonstrated on small animals, no one of these substances and no synthetic substance possesses all the effects of a potent cortical extract.

Adrenal cortex extracts have been assayed in many ways. There

formity of potency, these methods express the activity of adrenal cortex preparations in terms of dog units based on their ability to maintain the life of adrenalectomized dogs. An alternate assay method using adrenalectomized rats according to the procedure of Cartland and Kuizenga (*Am J Physiol.* 117:678, 1936) also may be employed and the results transposed into dog units, provided sufficient data are presented that such a comparison of assays is justified. No preparation of adrenal cortex extract will be accepted for inclusion in *New and Nonofficial Remedies* that does not have a minimum of 50 dog units or 25 rat units per 1 cc. of extract when assayed by the Cartland and Kuizenga method.

The Adrenal Steroids.—There have been isolated from the cortex crystalline compounds that are capable of maintaining the life of adrenalectomized animals and restoring toward normal the disturbed metabolic conditions induced by adrenal insufficiency. These compounds are steroids.

The chemical structure of the cortical steroids is related closely to that of the sex hormones; in fact, some of the cortical steroids have estrogenic or androgenic properties and in certain abnormal conditions of the cortex large amounts of androgens, and occasionally estrogens, may be recovered in the urine. On the other hand, the sex hormone progesterone has life-maintaining properties in adrenal insufficiency in small animals, while other sex hormones such as estrone and testosterone are capable of inducing slight electrolyte changes similar to those produced by cortical steroids. The steroids of the adrenal cortex may be divided structurally into the 11-desoxysteroids and the 11- and 11, 17-oxysteroids. Desoxycorticosterone belongs to the first class and, as its name indicates, lacks an oxygen atom at position 11 in the steroid nucleus. Its activity is limited chiefly to the electrolyte and water regulating function (mineralo-corticoid or sodium retaining hormone). The addition of oxygen at position 11 apparently is accompanied by potentiality for regulation of gluconeogenesis (gluco-corticoids), but the most potent compounds, cortisone and hydrocortisone, possess an oxygen atom also at position 17 (11, 17-oxysteroids). These three compounds, desoxycorticosterone, cortisone and hydrocortisone, have been prepared synthetically and are used clinically.

The adrenal cortex also plays a role in gluconeogenesis and, therefore, enters into the regulation of carbohydrate, fat and protein metabolism. Cortisone and hydrocortisone possess these powers to the greatest degree among isolated adrenal steroids. From in vivo studies it appears that hydrocortisone (compound F) may be the principal glucogenic steroid secreted by the adrenal cortex. In addition to their metabolic regulatory role, hydrocortisone and cortisone also regulate electrolyte exchange in the kidney tubules, but to a lesser degree than desoxycorticosterone.

With the availability of cortisone and hydrocortisone, extracts of the adrenal cortex, which formerly were the only preparations available, are required less frequently. Their principal indication is in the treatment of acute adrenal insufficiency.

ADRENAL CORTEX EXTRACT.—ADRENAL CORTEX INJECTION—U.S.P.—"Adrenal Cortex Injection is a sterile solution in

Physical Properties.—Adrenal cortex extract is a water-soluble extract obtained following extraction of the adrenal glands with fat solvents. Each cubic centimeter is obtained from not less than 40 Gm. of gland and contains not less than 50 dog units. The activity of the extract is relatively stable, especially if maintained at refrigerator temperature. Alcohol 10 per cent is used as a preservative.

Actions and Uses.—Although the extract is active by mouth, this method of administration is not to be depended on for therapeutic purposes. The usual methods of administration are subcutaneous, intramuscular or intravenous injection. The extract is of value in the treatment of Addison's disease and other types of adrenal insufficiency, and in surgical procedures involving the adrenal cortex when prophylactic measures are needed to prevent the development of temporary adrenal insufficiency. Aqueous adrenal cortical extracts may be of value in the treatment of acute stress

are of definite value in supplementing adrenal cortex extracts.

ARMOUR LABORATORIES

Solution Adrenal Cortex Extract. 10 cc. vials. Each cubic centimeter contains 3 mg. of extractive solids, with a biologic activity equivalent to 0.1 mg. of 17-hydroxycorticosterone. The solids are mainly a mixture of the physiologically active cortical steroids. It is physiologically standardized on adrenalectomized rats by using 17-hydroxycorticosterone and determining liver-glycogen deposition. Preserved with 10 per cent alcohol.

U. S. patent 2,096,342

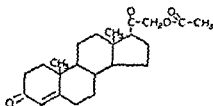
THE UPJOHN COMPANY

Solution Adrenal Cortex Extract. 10 and 50 cc. vials. 50 dog units per cubic centimeter. Each cubic centimeter contains not more than 3 mg. of gland extractives, having a potency equivalent

to 50 dog units when assayed by the Cartland-Kuizenga method, in physiologic solution of sodium chloride. Preserved with 10 per cent alcohol.

U. S. patent 2,096,342.

DESOXYCORTICOSTERONE ACETATE-U.S.P.—Doca Acetate (ORGANON).—Desoxycortone Acetate.—17-(β)-[1-Keto-2-acetoxyethyl]- Δ^4 -androstene-3-one—The structural formula of desoxycorticosterone acetate may be represented as follows:



Physical Properties.—Desoxycorticosterone acetate is a white, crystalline powder. It is odorless and is stable in air. It is practically insoluble in water. It is sparingly soluble in alcohol, acetone and in dioxane. It is slightly soluble in vegetable oils.

Actions and Uses.—Desoxycorticosterone has been isolated from the adrenal cortex in small amounts and is known as the acetate. Desoxycorticosterone has a biological activity.

Desoxycorticosterone acetate has no experimental glucocorticoid or androgenic activity or on the known activity is limited to the metabolism of sodium, potassium and water and is mediated through its action on the renal mechanism. It causes an increase in sodium ion and water retention.

Desoxycorticosterone acetate causes a decrease in blood pressure and increase in blood volume.

Desoxycorticosterone acetate, despite its limited range of physiologic activity, may be used in the management of adrenal insufficiency, both in maintenance and in the treatment of crises. Many patients with chronic adrenal insufficiency are enabled to resume normal activity by the administration of desoxycorticosterone acetate and sodium chloride alone. However, most clinicians prefer the use of cortisone or hydrocortisone with supplemental sodium chloride for the treatment of Addison's disease; desoxycorticosterone in small doses also may be used as a supplement. In the treatment of patients with acute adrenal insufficiency, aqueous adrenal cortical extracts, the gluco-corticoids and desoxycorticosterone all are employed.

Significant toxicity results from excessive amounts of desoxycorticosterone acetate. The most frequent signs are edema, pulmonary congestion, cardiac dilatation and failure. Arterial hypertension develops in about 30 per cent of patients with chronic adrenal insufficiency after treatment for several months or years. This may require a cautious reduction in the dosage of the steroid or salt or both. Occasionally toxicity due to decrease in serum potassium concentration is associated with sudden attacks of weakness and characteristic changes in the electrocardiogram.

Dosage.—The dosage of desoxycorticosterone acetate required for maintenance varies from 1 to 7 mg. daily. It depends primarily on individual variation and on the amount of sodium salts in the diet; i.e., the higher the salt intake the lower the requirement of the adrenal steroid. Experience indicates that most patients require about 3 mg. daily when taking 3 to 6 Gm. of sodium chloride in addition to that contained in the normal diet.

In the management of acute adrenal crises, 10 to 15 mg. may be required twice a day for 1 or 2 days in conjunction with liberal quantities of whole adrenal cortical extract or cortisone and with one or two daily infusions of 1,500 cc. of 5 per cent dextrose in isotonic sodium chloride solution. Transfusion of whole blood or plasma also may be indicated to combat shock.

Desoxycorticosterone acetate is insoluble in water and usually administered in oil by subcutaneous or intramuscular injection. After the maintenance dose has been determined carefully, pellets may be implanted subcutaneously to avoid repeated injections. A pellet of 0.12 Gm. is absorbed slowly, exerting an effect approximately equivalent to that of daily injections of 0.5 mg. Desoxycorticosterone pellets usually are effective for 9 to 13 months. Symptoms of adrenal insufficiency begin to recur when the pellets have been absorbed completely. Crumbling of pellets may result in increased absorption and, consequently, overdosage.

ORGANON, INC.

Solution Does Acetate in Oil: 1 cc. ampuls and 10 cc. vials. A solution in sesame oil containing 5 mg. of desoxycorticosterone acetate in each cubic centimeter.

U. S. patent 2,312,431. U. S. trademark 372,214.

Glucocorticoids

The two principal adrenal steroids concerned in gluconeogenesis and members of the 11, 17-oxysteroid series are hydrocortisone and cortisone. Their activity essentially is similar, although hydrocortisone probably is more active, weight for weight, and is less irritating to the synovial membranes when injected into joint spaces. The carbohydrate-regulating hormones of the adrenal cortex have been called glucocorticoids, and for convenience this term will be utilized to designate cortisone and hydrocortisone in the following discussion, as they are the sole members of the group available commercially.

When injected into adrenalectomized animals, the gluco-corticoids maintain life and resistance to various forms of stress ordinarily lethal to the unprotected adrenalectomized animal. The gluco-corticoids affect fat, protein and carbohydrate metabolism promoting gluconeogenesis, hyperglycemia and glycosuria and negative nitrogen balance unless adequate protein is supplied. They inhibit the activity of the lymphatic system, producing lymphopenia and reduction in the size of enlarged lymph nodes. In comparison with desoxycorticosterone, which is an adrenal corticoid of the 11-desoxy series, cortisone and hydrocortisone induce only mild sodium retention and potassium excretion, but large doses given over a period of several days may alter the electrolyte balance profoundly. Hydrocortisone and cortisone increase urinary excretion of creatine and uric acid but do not change creatinine excretion. The effect on renal excretion of calcium and phosphorus is variable.

Therapeutic dosages of the gluco-corticoids in the human being inhibit the production of corticotropin by the pituitary and depress the function of the adrenal cortex. Continued use of the hormones causes atrophy of the thymus and varying degrees of atrophy of the adrenal cortex. On sudden cessation of therapy, the adrenal cortex usually recovers from the partial atrophy and depression of function induced by the gluco-corticoids, but the danger of re-

particularly if they have been given in large doses for a few days, and the patient observed for signs of deficient adrenocortical function. Clinically, this depression of cortical function may be manifested by lassitude, weakness and lethargy. Surgical or medical emergencies during this period of reduced adrenal function require prompt re-employment of the gluco-corticoids (or corticotropin, if the adrenal cortex is capable of response) to enable the patient to survive the stress. Because of the effects on electrolyte balance, laboratory and metabolic studies should be performed before and during protracted therapy with cortisone and hydrocortisone. Measurement of fluid intake and output and daily weighing may give early indication of fluid retention. It may be wise to maintain the patient on an intake of less than 1 Gm. of sodium per day with supplemental potassium.

Significant increase in blood pressure may result from therapeutic doses of gluco-corticoids when antecedent vascular or renal damage is present or when retention of sodium and water develops.

When the gluco-corticoids are administered to patients over extended periods, they may cause widespread physiologic and metabolic effects resembling those encountered in Cushing's syn-

cutaneous striae, impairment of glucose tolerance, negative nitrogen balance, increased corticosteroid excretion, hypochloremic-hypopotassemic alkalosis and mental disturbance. The thin skin,

ecchymoses and polycythemia of Cushing's syndrome so far have not often been induced by therapy.

The negative nitrogen balance induced by high-dosage glucocorticoid therapy may delay bone and wound healing.

The glucocorticoids also may reactivate latent tuberculosis, and higher doses of antibiotics may be required to control co-existent bacterial infections than ordinarily would be necessary. Recurrence and activation of peptic ulcer has been reported during glucocorticoid therapy.

Cortisone and hydrocortisone have various effects on the nervous system. Usually, the patient experiences a feeling of well-being and euphoria. In some instances psychoses have developed, both manic and depressive states have been reported. Alterations in electroencephalographic patterns have been noted. There is evidence which suggests that they possess analgesic effect or increase the patient's capacity to bear pain.

The glucocorticoids are indicated chiefly for substitution therapy in frank adrenal insufficiency, such as may be encountered in Addison's disease, panhypopituitarism and after adrenalectomy, and in certain acute conditions where the period of treatment is not long enough to incur the metabolic effects of protracted therapy, i.e., to prevent shock in patients with adrenocortical tumors who are to undergo surgery of the adrenal glands. It is indicated also in the adrenogenital syndrome. Saline suspension parenterally and oral tablets of the hormones or their esters have been employed successfully, both alone and conjointly with desoxycorticosterone

states such as sodium chloride, sodium phosphate and sodium citrate.

in the so-called collagen group of diseases—rheumatoid arthritis, disseminated lupus erythematosus, periarteritis nodosa, dermatomyositis and scleroderma—their effects in these diseases in most instances obtain only during therapy. The mechanism of action appears to be a nonspecific anti-inflammatory effect.

is a function of the time-dosage relationship, therefore, minimal dosage schedules should be employed.

These hormones induce prompt recession of acute symptoms and

signs of acute rheumatoid arthritis, including local redness, swelling and tenderness. After 1 to 2 weeks of treatment, the sedimentation rate usually falls to nearly normal levels and rheumatic nodules regress. However, histologic examination of synovial tissue after several months of therapy has continued to disclose evidence of active rheumatoid arthritis. Following the withdrawal of the hormones, symptoms generally reappear within a short period, rarely longer than a few weeks. Continuation of therapy, even on reduced dosage schedules, may lead to the development of a state resembling Cushing's syndrome. The period of remission obtained by use of these hormones should be employed to begin active physiotherapeutic management of the patient. The acetate esters of cortisone and hydrocortisone may be injected into affected intra-articular spaces for local relief of pain and stiffness in both rheumatoid arthritis and osteoarthritis. Hydrocortisone acetate apparently produces a more prolonged and intense local effect with less irritation than does cortisone acetate.

Acute rheumatic fever has shown encouraging response to glucocorticoid therapy, especially in cases of short duration. Although the end results in the development of subsequent rheumatic valvular disease have not been evaluated, the fever, toxicity and arthralgia respond well to administration of the hormone, although the relief of acute symptoms is no more prompt than with adequate doses of acetylsalicylic acid. The glucocorticoids must be used with caution in acute rheumatic fever because the tendency to sodium and water retention may induce or aggravate cardiac failure before the hormone's beneficial results are manifested.

Cortisone and hydrocortisone are also effective in the treatment of

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reinstitution of treatment. Neoplastic diseases of the lymphatic system, such as lymphosarcoma, lymphatic leukemia and Hodgkin's disease, show temporary response to glucocorticoid therapy in some cases, but acute monocytic leukemia and chronic myelogenous leukemia appear to respond unfavorably.

The glucocorticoids may be employed for relief of symptoms in

of hemorrhage and perforation is borne in mind

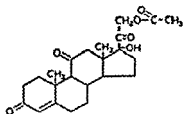
Cortisone and hydrocortisone are such potent hormonal agents that it is advisable to perform laboratory studies periodically as a safeguard against the danger of electrolyte imbalance.

The glucocorticoids are active by oral, parenteral or topical application. The ratio of oral to parenteral dosage is approximately 1:1. The oral route elicits more rapid but less sustained response and, therefore, requires repeated administration of the

hormones at 6-hour to 8-hour intervals. Prompt effects cannot be achieved by intramuscular injection of the suspensions; oral or intravenous injection may be required.

The hormones are contraindicated in long-term treatment of any condition complicated by hypertension, diabetes mellitus, congestive heart failure, mental disturbances, chronic nephritis and active or questionably healed tuberculosis. In large dosage they may mask the onset of an acute condition requiring surgery or reactivation of a latent chronic infection. There is evidence to suggest that the gluco-corticoids reduce the resistance of the host to certain infectious processes, such as tuberculosis and some virus diseases. They also have been reported to cause rapid spread of metastatic carcinoma.

CORTISONE ACETATE—U.S.P.—Cortogen Acetate (SCHERING) — Cortone Acetate (SHARP & DOHRME) — 11-Dehydro-17-hydroxycorticosterone-21-acetate — The structural formula for cortisone acetate may be represented as follows.



Physical Properties.—Cortisone acetate is a white, odorless powder. It melts with decomposition between 242 and 248°. It is practically insoluble in water, slightly soluble in ether and alcohol and freely soluble in chloroform.

Actions and Uses.—See the general statement on gluco-corticoids.

Cortisone acetate may be used for the control of systemic diseases by parenteral administration of the suspension or by oral ingestion of the tablets. For ophthalmic use, local instillation or injection of suspensions of varying concentrations or application of an ointment have proved effective.

Dosage.—Dosage does not depend as much on the specific diagnosis as on the acuteness, the prognosis and the expected duration of the disorder. In chronic disease of good prognosis, it is usually desirable to employ the lowest dosage that will provide adequate but not necessarily complete suppression of symptoms. On the other hand, when the condition is grave and the prognosis poor, it may be essential to employ much higher dosages. In acute disorders of short duration, it is permissible to use a relatively high dosage. Thus 80 to 100 mg per day may be administered initially in a chronic nonfatal disorder (such as rheumatoid arthritis, chronic asthma, or certain chronic ocular diseases); 200 to 400 mg or more per day initially in acute disorders (such as severe seasonal asthma, status asthmaticus, rheumatic fever).

Dosage should be reduced gradually, using larger decrements (100 mg) with larger totals and smaller decrements (10 to 15 mg) with total dosage of 100 mg. or less per day. For optimum response in severe disorders, as much as 0.3 Gm. may be administered the first day, followed by 0.2 Gm. the second day and then 0.1 Gm. daily. Injections of the parenteral solution should be made deep into the gluteal muscles. The daily dose should be divided into three or four equal parts for oral administration. Dosage should be reduced gradually to the minimum regimen that produces the desired response. To avoid undesirable side effects in chronic cases it is advantageous to interrupt treatment for 2 or 3 weeks whenever possible at intervals of 6 to 8 weeks.

In Addison's disease cortisone acetate may be employed in doses of 5 mg. to 20 mg. daily, either alone or combined with desoxycorticosterone and sodium chloride.

SCIHERING CORPORATION

Ophthalmic Suspension Cortogen Acetate: 5 cc. dropper bottles. A buffered suspension containing 5 or 25 mg. of cortisone acetate in each cubic centimeter. Preserved with benzalkonium chloride 1:5,000.

Suspension Cortogen Acetate: 10 cc. vials. A suspension containing 25 mg. of cortisone acetate in each cubic centimeter. Preserved with thimerosal 1:10,000.

Tablets Cortogen Acetate: 5 and 25 mg.

U. S. trademark 548,401.

SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Ophthalmic Ointment Cortone Acetate: 3.5 Gm. tubes. An ointment containing 15 mg. of cortisone acetate in each gram.

Ophthalmic Suspension Cortone Acetate: 5 cc. dropper bottles. An isotonic, buffered suspension containing 5 or 25 mg. of cortisone acetate in each cubic centimeter. Preserved with 0.02 per cent benzalkonium chloride and 0.5 per cent benzyl alcohol.

Suspension Cortone Acetate: 10 cc. vials. A suspension containing 50 mg. of cortisone acetate in each cubic centimeter.

20 cc. vials. A saline suspension containing 25 mg. of cortisone acetate in each cubic centimeter. Preserved with 0.9 per cent benzyl alcohol.

Tablets Cortone Acetate: 5 mg. and 25 mg.

U. S. trademark 531,347.

THE UPJOHN COMPANY

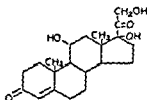
Ophthalmic Ointment Cortisone Acetate: 3.9 Gm. tubes. An ointment containing 15 mg. of cortisone acetate in each gram.

Suspension Cortisone Acetate with Benzyl Alcohol 1.5%: 20 cc.

vials. An isotonic saline suspension containing 25 mg. of cortisone acetate in each cubic centimeter.

Tablets Cortisone Acetate. 5, 10 and 25 mg.

HYDROCORTISONE—U.S.P.—Cortef (UPJOHN).—Cortril (PFIZER)—Hydrocortone (SHARP & DOHME)—17-Hydroxycorticosterone—The structural formula of hydrocortisone may be represented as follows



Physical Properties.—Hydrocortisone is a white, odorless powder which melts between 215 and 220° (with decomposition). It is freely soluble in dioxan and in methanol and very slightly soluble in ether and in water. The approximate amounts that dissolve in the following solvents to form 100 cc of solution are, 1.8 Gm. in alcohol and 0.4 Gm. in chloroform.

Actions and Uses.—See the general statement on gluco-corticoids. The topical uses of hydrocortisone are the same as those listed in the monograph for hydrocortisone acetate.

The physiologic and therapeutic effects of hydrocortisone are qualitatively similar to those of cortisone. Comparative clinical studies in patients with rheumatoid arthritis tend to indicate that hydrocortisone is therapeutically effective in smaller doses than cortisone, however, it has not been demonstrated that the incidence of undesirable metabolic or hormonal effects is minimized by the use of hydrocortisone as compared with cortisone.

Hydrocortisone is absorbed readily following oral administration, the effects of oral medication are manifest in 3 to 10 hours and persist about 12 to 14 hours. Its onset and duration of anti-rheumatic action seems comparable with that of cortisone.

Hydrocortisone is administered also by intravenous infusion when rapid effect or close control of dosage is required and when the oral route or intramuscular injection of the acetate is impractical, for example, if the patient is in shock, vomiting, or seriously ill. Intravenous infusion is indicated during the acute phase of status asthmaticus, allergic emergencies such as laryngeal edema and drug sensitivity, Addisonian crisis, disseminated lupus erythematosus crisis and in patients undergoing adrenalectomy.

Dosage.—Hydrocortisone is administered orally, by intravenous infusion, or topically as a 1 or 2.5 per cent lotion or ointment.

When given orally, daily observation is essential to determine individual response and to establish maintenance dosage. Routine

determinations of blood pressure and body weight, as well as a urinalysis, electrocardiogram and complete blood count, are essential. Occasionally, such special studies as blood sugar, carbon dioxide combining power and blood electrolytes are advisable. The dosage should be adjusted to the minimum amount that will provide relief adequate for rehabilitation; this adjustment may minimize or avoid the side-effects. Studies have indicated that the clinically

mately two-th

the response of a patient and the nature of the disease. For rheumatoid arthritis, the initial average adult daily dosage is 40 to 80 mg. given in divided doses, four times a day, until the desired effect is obtained (not over 2 weeks); the dosage then is reduced by steps of not more than 10 mg. to the minimum effective maintenance level. Withdrawal of treatment should be accomplished by similar gradual reduction. Variations in the daily maintenance dosage should be adjusted to meet the natural fluctuations of the disease, and, occasionally, therapy should be withdrawn long enough to determine whether remission has occurred.

The appearance of exaggerated hormonal effects may require withdrawal of therapy. The drug should not be withdrawn from patients undergoing major surgery or severe physical stress; they even may require increased dosage. With prolonged therapy, restriction of sodium and administration of potassium chloride may be necessary to maintain electrolyte balance. Temporarily, the cautious use of diuretics may be indicated, but these may provoke a further dangerous loss of potassium. In patients with diabetes mellitus, insulin requirements may be increased. Activity should be restricted in cardiovascular disease.

Continued supervision of patients is essential after discontinuation of therapy because the drug may continue to act for some time after the last dose. A temporary hypoadrenal state, manifested by weakness and hypoglycemia, may occur after abrupt withdrawal, but return of adrenal function may be expected within 2 weeks.

When given by intravenous infusion, hydrocortisone may be administered in a solution of isotonic sodium chloride, 5 or 10 per cent dextrose or 5 per cent gelatin containing not more than 0.2 mg. per cubic centimeter. Unused portions or cloudy solutions should be discarded. When protected from heat and light, the solution is stable for 12 months in closed containers. The dosage is determined by the rate of flow of the infusion. A rate of 4 mg. per hour for 24 hours usually produces physiologic effects equivalent to a daily oral dose of 200 mg. of cortisone acetate; 10 to 12 mg. per hour for 8 hours physiologic response equivalent to a daily 500 mg. of cortisone acetate in accordance with the response muscular or oral cortisone necessary to maintain the effects of hormone therapy, it should be given sufficiently in advance to allow time for absorption.

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

Ointment Cortril: 5 Gm. tubes. An ointment containing either 10 or 25 mg. of hydrocortisone in each gram.

14 2 Gm. tubes. An ointment containing 10 mg. of hydrocortisone in each gram. Both sizes preserved with 0.18 per cent methylparaben and 0.002 per cent propylparaben

Tablets Cortril: 10 and 20 mg.

U. S. patent 2,658,023

SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Lotion Hydrocortone: 15 cc. bottles. A lotion containing 10 mg. of hydrocortisone in each cubic centimeter. Preserved with 0.15 per cent sodium methyl *p*-hydroxybenzoate

Tablets Hydrocortone, 5, 10 and 20 mg.

U. S. trademark 536,023.

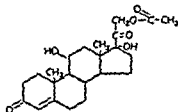
THE UPJOHN COMPANY

Infusion Cortef (Concentrate): 20 cc. ampuls. A solution in 50 per cent alcohol containing 5 mg. of hydrocortisone in each cubic centimeter.

Tablets Cortef: 5, 10 and 20 mg.

U. S. trademark 583,191.

HYDROCORTISONE ACETATE—U.S.P.—Cortef Acetate (UPJOHN). —Cortril Acetate (PFIZER) —Hydrocortone Acetate (SHARP & DOHME) —17-Hydroxycorticosterone-21-acetate. —The structural formula of hydrocortisone acetate may be represented as follows:



Physical Properties.—Hydrocortisone acetate is a white, odorless solid. It melts between 218 and 223° (with decomposition). It is very slightly soluble in ether and practically insoluble in water. The amounts that dissolve in the following solvents to form 100 cc. of solution are 0.45 Gm. in alcohol and 0.73 Gm. in chloroform.

Actions and Uses.—See the general statement on gluco-corticoids. When injected systemically, hydrocortisone acetate is capable of producing the same side effects as cortisone acetate. However, when administered by intrasynovial injection, systemic side effects have not been observed.

Hydrocortisone acetate is useful for topical application in the

During the growth of the ovarian follicles induced by the follicle-stimulating hormone of the anterior pituitary, an estrogenic hormone secreted by the follicles (probably from the cells of the theca interna), evokes certain changes in the accessory organs. The vaginal mucosa thickens and the cells undergo a more intense cornification; the myometrium hypertrophies, while the endometrium rapidly becomes proliferated. At this time the duct system of the breast develops. At ovulation there is a release of the luteinizing

hormone. Estrogen also is low at this time. The intrinsic factors that cause extravasation of blood and tissue fragmentation at the end of the cycle are not yet clear, but involve spasm of the spiral arteries of the endometrium with ischemia, endometrial necrosis and subsequent venous bleeding.

Estrogen.—The injection of potent estrogenic substances in castrated animals will induce in the accessory sex organs changes typical of estrus. Long-continued injections, however, induce hypertrophic, and then frequently metaplastic, changes in the uterus, cervix and breast. Clinical endometrial hyperplasia, chronic cystic mastitis and fibromyomas may be due to long-continued estrogen secretion by the ovary.

Estrogenic substance also is responsible for the contractility of the uterus and the sensitivity of the myometrium to oxytocic agents. The smooth muscle of the human fallopian tube also is responsive to estrogenic substance.

The curve of excretion of estrogenic substances in normally menstruating women varies extremely from day to day. In general, however, there is at least one sudden peak at the height of follicular activity during ovulation. Excretion curves in ovarian disorders have not been studied adequately because of technical difficulties in assays. Several methods for the chemical assay of estrogens have been introduced recently. During pregnancy large amounts of estrogens are excreted in the urine in the form of water-soluble conjugate. In pregnant women these are preponderantly in the form of glucuronides, and in pregnant mares in the form of sulfates. Hydrolysis of the urine, either by acid or by putrefaction, converts the conjugated estrogens into their free forms, which are more active physiologically.

Estrogenic substances occur widely in nature, in plants as well as in animals. Estrone (ketohydroxyestrin) and estriol (trihydroxyestrin) are extracted from urine or placentas of humans during pregnancy while several estrogens, including estrone, equilin and hippulin, are obtained from the urine of pregnant mares. Sow's

the trans form; however, more recent analyses have demonstrated that it is estradiol-17 β , the cis form. Therefore, the substance that was originally called α -estradiol is in reality estradiol-17 β . Since estrogens are destroyed rapidly in the animal body, estrogen compounds which are absorbed slowly from the site of injection may be more efficient. Esters of the estrogens (benzoate, acetate, propionate, palmitate) have been prepared for this purpose.

Estrogens are used either orally, intravaginally or by hypodermic injection of a solution in oil or a colloidal suspension in an aqueous solvent. Estrone and estradiol lose considerable activity when taken orally. When estrone is administered in the form of its sulfate, it retains a greater amount of its potency. Several estrogenic compounds have been prepared which lose relatively little potency when administered orally. Since these are highly active, even when given once daily, they are to be preferred except when oral administration is contraindicated.

Preparations extracted from the urine of pregnant women or pregnant mares may contain crystalline or amorphous estrogenic material. The estrogenic activity of such extracts is due almost entirely to estrone. Synthetic estrogens, which vary in efficiency and severity of side effects, also are available. Physiologic difference between these compounds and the natural steroids has not been demonstrated.

An enormous amount of clinical research has been done with estrogenic substances. Favorable results have been obtained in only a few conditions.

Estrogenic substances are used in a variety of conditions associated with deficiency of estrogens. These include symptoms of the menopause syndrome natural or induced, senile vaginitis, kraurosis vulvae and pruritus vulvae. Some authorities suggest that estrogens may be given to control vasomotor symptoms of the menopause in doses sufficiently small not to produce endometrial or vaginal epithelial changes. A related use is in the treatment of hypogonitalism in the female, however the use of estrogen in such conditions substitutes for ovarian function but does not stimulate it. Estrogens have been used in attempts to inhibit production of gonadotropic hormone by the anterior pituitary. This requires very large doses. Large doses of estrogen probably do not inhibit lactation immediately postpartum, but estrogenic therapy is helpful in relieving the engorgement of breasts especially when lactation is to be suppressed. According to some investigators, estrogenic therapy does not clearly improve the results obtained with the usual measures, dehydration and breast feeding, and may be complicated by postpartum bleeding and a high rate of recurrence of engorgement.

It is possible to interrupt the prolonged or excessive flowing of many women with "functional bleeding" by brief courses of intensive estrogenic therapy. This is considered safe practice only when the interval of freedom from bleeding is used to eliminate local pelvic lesions as the cause of the flowing. The subsequent administration of sequences of estrogenic substances and progesterone to re-establish cycles of flowing is a possible method of allevi-

ating a condition that is widely believed to result from the deficiency of one or both ovarian hormones, but their value for the purpose must be regarded as incompletely established.

Estrogens cause undesirable uterine and vaginal growth and proliferation and frequently withdrawal endometrial bleeding. Since the advent of effective antibiotics, the use of estrogens no longer is indicated in the treatment of gonorrheal vaginitis in children.

Estrogenic materials act together with, or as a substitute for, castration in the palliation of the local discomforts from prostatic carcinoma and its metastases. The action apparently is not curative but may persist for a number of months.

Estrogens are contraindicated in animals which have an experimental mammary carcinoma. Estrogens are contraindicated, therefore, in the treatment of women who have a familial or personal history of mammary or genital malignancy. However, estrogens may be used in treatment of inoperable breast carcinoma.

Some estrogenic substances, notably diethylstilbestrol, ethinyl estradiol, dienestrol, estradiol dipropionate and conjugated estrogenic substances, have been found to exert, under certain conditions, a palliative effect on mammary cancer. Estrogens usually are ineffective if given to a woman with breast cancer if she is less than 50 years of age, or if the disease is

metastatic. In some patients, however, acceleration of the disease may occur, and should this be observed, therapy should be discontinued immediately. Estrogens can cause salt retention and edema which may be dangerous. Such reactions should be combated by a low salt diet and ammonium chloride or mercurial diuretics; if these methods are ineffective, therapy should be discontinued. Occasionally uterine bleeding may occur, particularly on cessation of therapy. Usually, this is not serious, but patients should be examined carefully to rule out concomitant uterine tumors, which are known to occur not infrequently in older patients with mammary cancer.

Progesterone.—The hormone of the corpus luteum induces secretory changes of the endometrium, stimulates growth of the mammary alveolar tissue and relaxes the uterine smooth muscle. It is essential for nidation of the ovum and maintenance of pregnancy. During gestation the ovary elaborates progesterone only through the third month, after which the placenta is responsible for its elaboration. Progesterone is excreted in the form of pregnandiol glycuronide and is found in the urine in pregnancy and during the corpus luteum phase of the normal cycle. Studies on habitual abortion have revealed that pregnandiol excreted in the urine may be abnormally low at about the hundredth day of gestation, indicating an insufficiency of progesterone. Daily administration of 10 to 50 mg. of progesterone sometimes brings the pregnandiol level to normal, but it has not been uniformly efficacious.

greater response is desired, parenteral therapy with injectable compounds may be used to start treatment, followed by oral maintenance therapy with estradiol alone. (See the monograph on estradiol benzoate.)

For the local treatment in the vagina, a suppository containing 0.4 mg inserted at bedtime is recommended for adults, in conjunction with systemic therapy. Smaller amounts formerly were used for local treatment of gonorrheal vaginitis in children, but this method has been abandoned since the advent of penicillin.

BIORGANIC LABORATORIES, INC.

Powder Estradiol: Bulk; 1, 5 and 10 Gm. containers for compounding use.

CHICAGO PHARMACAL COMPANY

Solution Estradiol in Oil: 1 cc ampuls and 30 cc. vials. A solution in sesame oil containing 0.14 and 0.28 mg in each cubic centimeter 10 cc vials. A solution in sesame oil containing 0.28 mg. of estradiol in each cubic centimeter. Preserved with 0.5 per cent benzyl alcohol.

Suspension Estradiol with Benzyl Alcohol 4%: 30 cc. vials. A suspension containing 0.14 and 0.28 mg in each cubic centimeter. 1 cc. ampuls. A microsuspension containing 0.14 mg. of estradiol in each cubic centimeter.

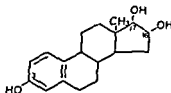
1 cc. ampuls and 10 cc. vials. A microsuspension containing 0.28 mg of estradiol in each cubic centimeter.

CIBA PHARMACEUTICAL PRODUCTS, INC.

Tablets Ovoclyn: 0.1, 0.2 and 0.5 mg.

U. S. patent 2,096,744 U. S. trademark 362,717

ESTRIOL.—Theelol—3,16,17-Trihydroxy- Δ -1,3,5-estratriene—A crystalline estrogenic steroid isolated from the urine of pregnancy. The structural formula of estriol may be represented as follows.



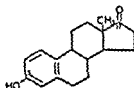
ble in water but is soluble in alcohol, dioxane and oils.
Actions and Uses.—Estriol is much less actively estrogenic than estrone when injected. See general statement on estrogen.

Dosage.—Orally, 0.06 to 0.12 mg. one to four times a day, alone or as supplement to parenteral therapy.

PARKE, DAVIS & COMPANY

Kapsals Theelol: 0.24 mg.

ESTRONE-U.S.P.—Estrugenone (KREIERS-URBAN).—Estrusol (CARROLL DUNHAM SMITH)—Thelestrin (CARRICK)—Theelin.—The structural formula of estrone may be represented as follows:



Physical Properties.—Estrone occurs as a white to creamy white, crystalline powder or as small, white crystals. It is odorless and is stable in air. It is soluble in alcohol, acetone, dioxane, vegetable oils and in solutions of fixed alkali hydroxides but only slightly soluble in water.

Actions and Uses.—See the general statement on estrogen.

Dosage.—In disturbances of the menopause 0.2 mg. to 1 mg. injected intramuscularly one or more times weekly depending on the response of the patient. After relief is obtained dosage may be lowered to a maintenance level. As much as 5 mg. per week may

ing and it is advisable to reduce the dose of estrone as soon as feasible.

Estrone is effective by mouth if the dosage is adequate.

ABBOTT LABORATORIES

Solution Estrone in Oil: 1 cc. ampuls. A solution in peanut oil containing 1 mg. of estrone in each cubic centimeter. 10 cc. vials in each cubic centimeter. 1 per cent chlorobutanol.

Aqueous Suspension Estrone: 1 cc. ampuls and 10 cc. vials. A suspension containing 2 mg. of estrone in each cubic centimeter. 5 cc. vials. A suspension containing 5 mg. of estrone in each cubic centimeter. Vial solutions are preserved with 0.9 per cent benzyl alcohol.

THE BIO-INTRASOL LABORATORIES, INC.

Solution Estrone in Oil with Benzyl Alcohol 2%: 1 cc. ampuls and 10 cc. vials. A solution in sesame oil containing 1 mg. of estrone in each cubic centimeter. Preserved with 0.3 per cent chlorobutanol.

Aqueous Suspension Estrone: 10 cc. vials. A suspension containing 2 mg. of estrone in each cubic centimeter. Preserved with 0.5 per cent phenol.

BIORGANIC LABORATORIES, INC.

Powder Estrone: Bulk; 1, 5 and 10 Gm. containers for compounding use.

G. W. CARRICK COMPANY

Solution Thelestrin in Oil: 1 cc. ampuls and 10 cc. vials. A solution in sesame oil containing 1 mg. of estrone in each cubic centimeter. The 10 cc. vial is preserved with 0.5 per cent benzyl alcohol.

Aqueous Suspension Thelestrin: 10 cc. vials. A suspension containing 1 mg. of estrone in each cubic centimeter

1 cc. ampuls and 10 cc. vials. A suspension containing 2 mg. of estrone in each cubic centimeter

10 cc. vials. A suspension containing 5 mg. of estrone in each cubic centimeter. The 10 cc. vials are preserved with thimerosal 1:10,000.

KREIERS-URBAN COMPANY

Solution Estrugenone in Oil: 1 cc. ampuls and 10 and 30 cc. vials. A solution in sesame oil containing 1 mg. of estrone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

10 cc. vials. A solution in sesame oil containing 2 mg. of estrone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Suspension Estrugenone with Procaine Hydrochloride 1%: 1 cc. ampuls and 10 cc. vials. A suspension in 15 per cent propylene glycol containing 2 mg. of estrone in each cubic centimeter. Preserved with thimerosal 1:10,000.

1 cc. ampuls and 5 and 10 cc. vials. A suspension in 30 per cent propylene glycol containing 5 mg. of estrone in each cubic centimeter. Preserved with 0.1 per cent sodium bisulfite and thimerosal 1:10,000.

U. S. trademark 377,549.

ELI LILLY & COMPANY

Aqueous Suspension Estrone: 1 cc. ampuls. A suspension containing 1, 2 or 5 mg. of estrone in each cubic centimeter.

10 cc. ampuls. A suspension containing 2 mg. of estrone in each cubic centimeter.

5 cc. ampuls. A suspension containing 5 mg. of estrone in each cubic centimeter. Preserved with thimerosal 1:10,000.

Solution Estrone in Oil: 1 cc. ampuls. A solution in sesame oil containing 0.5 or 1 mg. of estrone in each cubic centimeter

10 cc. vials. A solution in sesame oil containing 1 mg. of estrone in each cubic centimeter.

Vaginal Suppositories Estrone: 0.2 mg. of estrone in a glycerin base.

LINCOLN LABORATORIES, INC.

Solution Estrone in Oil with Benzyl Alcohol 2%: 10 and 15 cc. vials A solution in sesame oil containing 0.3 and 1 mg., respectively, of estrone in each cubic centimeter.

Aqueous Suspension Estrone with Benzyl Alcohol 2%: 10 cc vials An aqueous suspension containing 2 mg. of estrone in each cubic centimeter

MEYER CHEMICAL COMPANY, INC.

Solution Estrone in Oil: 10 cc. vials. A solution in sesame oil containing 1 mg of estrone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol

E S MILLER LABORATORIES, INC

Aqueous Suspension Estrone: 10 cc vials A suspension containing 2 or 5 mg of estrone in each cubic centimeter

PARKE, DAVIS & COMPANY

Solution Theelin in Oil. 1 cc ampuls A solution in peanut oil containing 0.2, 0.5 or 1 mg of estrone in each cubic centimeter. 10 cc. vials A solution in peanut oil containing 1 mg of estrone in each cubic centimeter

Aqueous Suspension Theelin: 1 cc ampuls A suspension containing 1, 2 or 5 mg of estrone in each cubic centimeter

5 cc vials A suspension containing 5 mg of estrone in each cubic centimeter.

10 cc vials A suspension containing 2 mg. of estrone in each cubic centimeter. The 5 cc and 10 cc vials are preserved with benzethonium chloride 1:10,000

Vaginal Suppositories Theelin 0.2 mg of estrone in a glycerogelatin base

PRIZER LABORATORIES, DIVISION OF CHAS PRIZER & COMPANY, INC.

Suspension Estrone 10 cc vials A suspension containing 2 or 5 mg of estrone in each cubic centimeter Preserved with 0.01 per cent thimerosal

CARROLL DUNHAM SMITH PHARMACEUTICAL COMPANY

Solution Estrusol in Oil 30 cc vials A solution in peanut oil containing 1 mg of estrone in each cubic centimeter Preserved with 0.5 per cent chlorobutanol

Aqueous Suspension Estrusol: 5 and 15 cc vials A suspension in isotonic sodium chloride solution containing 2 mg of estrone in each cubic centimeter

15 cc vials A suspension in isotonic sodium chloride solution containing 5 mg of estrone in each cubic centimeter Preserved with 0.5 per cent chlorobutanol

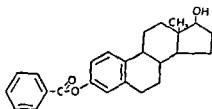
S J. TUTAG & COMPANY

Aqueous Suspension Estrone: 10 cc. vials. A suspension containing

2 or 5 mg. of estrone in each cubic centimeter. Preserved with 0.005 per cent and 0.01 per cent thimerosal, respectively.

Esterified Parent Estrogens

ESTRADIOL BENZOATE-U.S.P.—Dimenformon Benzoate (ORGANON)—Ovocylin Benzoate (CIBA).—Beta-estradiol benzoate.—Estradiol Monobenzoate.— Δ -1,3,5-Estratriene-17-ol-3-benzoate.—“Estradiol Benzoate is the benzoyl ester of the beta isomer of estradiol (3,17 β -diol-1,3,5-estratriene.” *U.S.P.* The structural formula of estradiol benzoate may be represented as follows:



Physical Properties.—Estradiol benzoate is a white or slightly yellow-to-brownish, crystalline powder. It is odorless and stable in air. It is almost insoluble in water, soluble in alcohol, slightly soluble in ether and sparingly soluble in sesame and other vegetable oils.

Actions and Uses.—Estradiol benzoate, one of the esters of estradiol, is less subject to destruction in the tissues than its parent compound, and thus it is suitable for parenteral injection, producing the same effects as estradiol (See the monograph on estradiol, the general statement on ovaries and the subsection on estrogen) Esterification of estradiol slows its rate of absorption and elimination, so that the relative efficiency of the injectable estradiol benzoate is greater than that of orally administered estradiol. Estradiol benzoate is subject to the same contraindications as other estrogens.

Dosage.—Estradiol benzoate is administered by intramuscular injection as a solution in oil. Doses are expressed in terms of the weight of the esters.

For treatment of the menopausal syndrome, the initial dosage, depending on severity of symptoms, ranges from 1 to 1.66 mg.

progesterone therapy. In breast engorgement, 1.66 mg daily is administered until the engorgement subsides. In kraurosis vulvae and senile vaginitis or pruritus vulvae, the dosage is the same as that indicated for the menopausal syndrome, except that this is administered with vaginal suppositories of prostatic carci-

CIBA PHARMACEUTICAL PRODUCTS, INC.

Solution Ovocycin Benzoate in Oil. 10 cc. vials. A solution in sesame oil containing 0.33 or 1.66 mg of estradiol benzoate in each cubic centimeter.

U. S. patent 2,033,487.

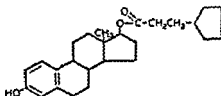
ORGANON, INC.

Solution Dimenformon Benzoate in Oil: 1 cc. ampuls. A solution in sesame oil containing 0.166, 0.33, 1 or 1.66 mg of estradiol benzoate in each cubic centimeter. Preserved with 0.8 per cent methylparaben and 0.1 per cent propylparaben.

10 cc vials. A solution in sesame oil containing 0.33 or 2 mg of estradiol benzoate in each cubic centimeter. Preserved with 0.8 per cent methylparaben and 0.1 per cent propylparaben.

U. S. trademark 365,455.

ESTRADIOL CYCLOPENTYLPROPIONATE.—3-Hydroxy- Δ -1,3,5-estratriene-17-cyclopentylpropionate.—The structural formula of estradiol cyclopentylpropionate may be represented as follows



Physical Properties.—Estradiol cyclopentylpropionate is a white, odorless, crystalline solid with a melting point between 148 and 152°. It is freely soluble in chloroform and in ether and practically insoluble in water and in alkalis. The approximate amounts that dissolve at 25° in the following solvents to form 100 cc. of solution are: 2 Gm. in alcohol and 2 Gm. in methanol.

Actions and Uses.—Estradiol cyclopentylpropionate has the same actions and uses as estradiol and its other fat-soluble esters (See the monographs on estradiol, estradiol benzoate and estradiol dipropionate.) In vegetable oil solutions for intramuscular injection, estradiol cyclopentylpropionate may produce more prolonged estrogenic effects than similar oil solutions of either estradiol benzoate or estradiol dipropionate. In menopausal women, the average duration of estrogenic action, as measured by vaginal smear, is approximately 3 to 4 weeks after a single injection of 5 mg. in oil. Relief of vasomotor symptoms appears within 1 to 5 days and is maintained 1 to 3 weeks.

Estradiol cyclopentylpropionate is not associated with adverse reactions to any greater extent than may be encountered with injectable oil solutions of other esters of estradiol. It should be employed with the same precautions as with the administration of similar preparations and of estrogens in general.

Dosage.—Estradiol cyclopentylpropionate is administered in oil

solutions by intramuscular injection only. Initially, a single dose of 1 to 5 mg. is injected weekly for 2 or 3 weeks; for maintenance, the dosage interval may be lengthened to 3 to 4 weeks.

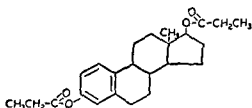
THE UPJOHN COMPANY

Solution Depo-Estradiol Cyclopentylpropionate in Oil: 10 cc. vials. A solution in cottonseed oil containing 1 mg. of estradiol cyclopentylpropionate in each cubic centimeter.

5 cc. vials. A solution in cottonseed oil containing 5 mg. of estradiol cyclopentylpropionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

U. S. patent 2,611,773 U. S. trademark 515,760.

ESTRADIOL DIPROPIONATE-U.S.P.—Ovocylin Dipropionate (CIBA).— Δ -1,3,5-Estratriene-3,17-dipropionate.—“Estradiol Dipropionate is the dipropionyl ester of the beta isomer of estradiol” U.S.P. The structural formula of estradiol dipropionate may be represented as follows:



Physical Properties.—Estradiol dipropionate forms small, white to off-white crystals. It is almost insoluble in water, soluble in acetone, alcohol and dioxane and sparingly soluble in vegetable oils. Estradiol dipropionate melts between 103 and 106°.

Actions and Uses.—Estradiol dipropionate, an ester of estradiol, is less subject to destruction in the tissues than the parent compound, is suitable for parenteral injection to produce the effects of that estrogen and shares the actions and uses of estrogens in general. Its contraindications are also the same as for other estrogens. See the monograph for estradiol, the general statement on the ovaries and the subsection on estrogen.

Estradiol dipropionate, like estradiol benzoate, is absorbed more slowly and eliminated less rapidly than estradiol, but its effects are qualitatively the same as those of other estradiol compounds. Also see the monograph on estradiol benzoate.

Dosage.—Estradiol dipropionate is injected intramuscularly as a solution in oil and is given in doses expressed in terms of the weight of the ester. A single dose is approximately half as potent by weight as estradiol benzoate, but, owing to its more sustained action, estradiol dipropionate is more potent than the benzoate when the two are compared on the basis of maintenance dosage required to provide equivalent therapeutic effects.

For the menopausal syndrome, the initial dosage ranges from 1 to 5 mg. injected weekly for two or three injections; maintenance

usually requires from 1 to 2.5 mg. every 10 to 14 days. For substitution therapy in hypogonitalism and sexual infantilism, 2.5 to 5 mg. weekly is recommended. For functional uterine bleeding, 5 mg. weekly is recommended followed by sequential progesterone therapy. In breast engorgement, 2.5 mg. daily is given until the condition subsides. The same doses as for the menopausal syndrome are applicable to kraurosis vulvae and senile vaginitis or pruritus vulvae.

CIBA PHARMACEUTICAL PRODUCTS, INC.

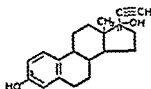
Solution Ovocylin Dipropionate in Oil. 1 cc. ampuls. A solution in sesame oil containing 0.2, 0.5, 1, 2.5 or 5 mg. of estradiol dipropionate in each cubic centimeter.

10 cc. vials. A solution in peanut oil containing 0.2, 1 or 5 mg. of estradiol dipropionate in each cubic centimeter.

U. S. patent 2,205,627.

Derivatives of Parent Estrogens

ETHINYL ESTRADIOL (Ciba).—Lynor.
Orestralyne (M).—3,17-dihydroxy
 ethinyl estradiol



Physical Properties.—Ethinyl estradiol is a fine, white, odorless, crystalline powder, which melts between 141 and 146°. On prolonged heating at 150° the melt sometimes solidifies. The polymorph thus obtained melts between 180 and 186°. It is soluble in acetone, alcohol, chloroform, dioxane, ether and vegetable oils, but practically insoluble in water. It is soluble in solutions of sodium or potassium hydroxide.

reactions, such as headache, nausea and vomiting, is found in the same proportion of patients as occurs with other orally active

estrogens. When the total daily dose is taken at bedtime the incidence of side reactions is reduced.

Dosage.—In hypo-ovarianism: 0.05 mg. one to three times daily during the first half of a cyclic estrogen-progesterone regimen. In menopause: 0.02 to 0.05 mg. one to three times daily.

For functional uterine bleeding (menometrorrhagia), 0.5 mg. once or twice daily. After hemostasis, 0.05 mg. one to three times daily as part of cyclic estrogen-progesterone therapy. The suggested course of therapy consists of three 30-day cycles exactly alike. The the h to itra-muscular injection of 5 mg. of progesterone. The treatment then is suspended, and after a latent period of about 5 days the patient generally begins to bleed again. Five additional days are allowed for this bleeding episode, and then the second cycle of treatment is begun.

In prostatic carcinoma, 0.15 to 3 mg. daily. For control of breast engorgement 0.2 to 1 mg. daily for 3 days, gradually decreasing to 0.1 mg. daily at the end of an additional 7 days.

CIBA PHARMACEUTICAL PRODUCTS

Tablets Eticlyol: 0.02 and 0.05 mg.

MCNEIL LABORATORIES, INC.

Elixir Orestralyne: 118.3 and 473 cc. and 3.78 liter bottles. A flavored alcoholic elixir containing 0.004 mg. of ethinyl estradiol in each cubic centimeter.

Tablets Orestralyne: 0.02, 0.05 and 0.5 mg.

U. S. trademark 560,766.

ORGANON, INC.

Elixir Lynoral: 118 and 473 cc. and 3.78 liter bottles. A solution containing 0.0075 mg. of ethinyl estradiol in each cubic centimeter. Preserved with 0.037 per cent methylparaben and 0.025 per cent propylparaben.

Tablets Lynoral: 0.01 and 0.05 mg.

SCHERING CORPORATION

Tablets Estinyl: 0.02, 0.05 and 0.5 mg.

U. S. patents 2,251,939 and 2,263,976 U. S. trademark 398,209.

VANPELT & BROWN, INC.

Tablets Oradiol: 0.02 and 0.05 mg.

U. S. trademark 568,045.

Conjugated Estrogens

ESTROGENIC SUBSTANCES, CONJUGATED.—Amnestrogen (SQUIBB).—Conestron (WYETH).—Estrifol (PREMO).—Konogen (LILLY).—Premarin (AYERST).—An amorphous preparation containing the naturally occurring, water-soluble, conjugated forms of the mixed estrogens obtained from the urine of pregnant mares. Conjugated estrogenic substances may be prepared by either selective extraction or selective adsorption of concentrated urine from mares pregnant 5 months or longer.

The principal estrogen present in conjugated estrogenic substances is sodium estrone sulfate. Varying small amounts of other equine estrogens and relatively large quantities of nonestrogenic material also are present in the mixture. The total estrogenic potency of the preparation is expressed in terms of an equivalent quantity of sodium estrone sulfate.

Actions and Uses.—See the general statement on estrogen.

Dosage.—For the control of menopausal symptoms, 1.25 mg daily is usually sufficient. If the response is not satisfactory after a few days of treatment, the dose may be increased. After symptoms have been brought under control the dosage may usually be reduced. For the treatment of senile vaginitis, kraurosis vulvae and pruritus vulvae, 1.25 to 3.75 mg daily should be sufficient. For palliation of mammary cancer, a daily oral dose of 30 mg is recommended.

AYERST LABORATORIES, INC

Liquid Premarin: 120 cc bottles. A 12.5 alcohol solution containing 0.16 mg of conjugated estrogenic substances in each cubic centimeter.

Tablets Premarin: 0.63, 0.3, 1.25 and 2.5 mg.

U. S. trademark 397,925

ELI LILLY & COMPANY

Tablets Konogen: 0.625, 1.25 and 2.5 mg.

PREMO PHARMACEUTICAL LABORATORIES, INC

Tablets Estrifol: 1.25 mg.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATTHEWSON CHEMICAL CORPORATION

Tablets Amnestrogen: 0.3, 0.62, 1.25 and 2.5 mg.

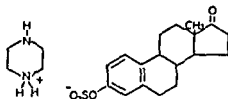
U. S. trademark 329,313

WYETH LABORATORIES, INC.

Tablets Conestron: 0.62 and 1.25 mg.

U. S. trademark 422,035

PIPERAZINE ESTRONE SULFATE—Sulastrox Piperazine (Abbott).—Piperazine estrone sulfate marketed for use as a drug is stabilized with a small amount of free piperazine. The structural formula of piperazine estrone sulfate may be represented as follows.



Physical Properties.—Piperazine estrone sulfate is a fine, white to creamy white, odorless, crystalline powder. It melts between 185 and 195° to a light brown syrup, which solidifies on further heating, and finally melts with decomposition between about 240 and 250°. It is slightly soluble in water and alcohol.

Actions and Uses.—Piperazine estrone sulfate has the same actions and uses as the naturally occurring conjugated estrogens. See the general statement on estrogens.

Dosage.—Piperazine estrone sulfate is administered orally. For the control of menopausal symptoms, 1.5 mg. daily usually is sufficient. The dosage may be increased if the response is not satisfactory; it may be reduced gradually when the symptoms have been controlled. For the treatment of senile vaginitis, kraurosis vulvae and pruritus vulvae, 1.5 to 4.5 mg. should be adequate. For postpartum breast engorgement, 4.5 mg. is administered at 4-hour intervals for five doses.

ABBOTT LABORATORIES

Elixir Sulestrex Piperazine: 118 cc. bottles. A flavored elixir containing 0.3 mg. of piperazine estrone sulfate in each cubic centimeter.

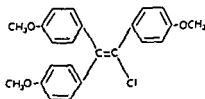
Tablets Sulestrex Piperazine: 0.75, 1.5 and 3 mg.

U. S. patent 2,642,427 U. S. trademark 560,753.

Nonsteroid Estrogens

Stilbene Derivatives

CHLOROTRIANISENE (4,4'-dichloro-2,2'-bis(4-methoxyphenyl)-5,5'-dihydrostilbene)
 formula of



Physical Properties.—Chlorotrianisene is a white, odorless, crystalline powder with a melting point between 114 and 117° (becomes syrupy at about 108°). It is freely soluble in acetone,

benzene and chloroform and very slightly soluble in water. The amounts that dissolve in the following solvents to form 100 cc. of solution are 0.28 Gm. in alcohol and 3.6 Gm. in ether.

Actions and Uses.—Chlorotrianisene in general shares the actions and uses of the estrogens (see the general statement on estrogens). However, it possesses certain peculiar attributes not common to other estrogens. When administered orally, the amount of estrogenic activity recovered in the stool exceeds the amount originally administered in the form of chlorotrianisene. This indicates that by some metabolic process the potency of the drug is enhanced. A hint at the probable locale of this enhancement is furnished by experiments in which the activity of chlorotrianisene is increased by incubation with liver homogenates. Chlorotrianisene, in the dosages used in experimental studies on laboratory animals, apparently induced less pituitary or adrenal hyperplasia than other estrogens. The compound is stored in the body fat, from which it is released slowly over a period of time, varying with the amount administered. Therefore, its action will persist for varying periods following discontinuance of the drug. Its use in high dosages in mammary cancer occurring 5 years or more past the menopause is not recommended because of the occurrence of uterine bleeding, although there is less tendency toward withdrawal bleeding in the lower dosage recommended for the menopause. Chlorotrianisene is effective in the relief of breast engorgement. It apparently causes a minimal incidence of withdrawal bleeding.

Dosage.—Chlorotrianisene has a lower milligram equivalent than other synthetic estrogens and doses are higher for comparable effects. The average dose for relief of menopausal symptoms varies between 12 and 24 mg. daily by mouth. In prostatic cancer, 24 mg. daily has proved effective in relieving symptoms. The average recommended dose for the relief of breast engorgement is 48 mg. of chlorotrianisene daily for 7 days.

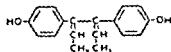
THE WAT S. MERRELL COMPANY

Capsules TACE: 12 mg. in corn oil.

Oral Drops TACE. 30 cc. bottles. A flavored solution in vegetable oil containing 12 mg. of chlorotrianisene in each cubic centimeter.

U. S. patent 2,430,891

DIENESTROL-U.S.P.—*Restrol* (CENTRAL)—3,4-Bis(*p*-hydroxyphenyl)-2,4-hexadiene—"Dienestrol, dried at 105° for 2 hours, contains not less than 98 per cent of $C_{18}H_{18}O_2$." U.S.P. The structural formula of dienestrol may be represented as follows:



Physical Properties.—Dienestrol forms colorless or white or practically white, needlelike crystals or a white or practically white crystalline powder. It is odorless and melts between 231 and 234°.

It is readily soluble in acetone, alcohol, ether, methanol and propylene glycol and in dilute aqueous sodium hydroxide; it is soluble in chloroform and practically insoluble in water and dilute mineral acids.

Actions and Uses.—Dienestrol is used orally. Investigation indicates that this compound gives rise to fewer side reactions than diethylstilbestrol and related synthetic estrogens, but it is less potent (See the general statement on estrogen.)

Dosage.—In the treatment of menopausal symptoms, orally in daily doses of 0.1 to 0.5 mg. for mild to moderately severe symptoms; or 2.5 to 5 mg. injected subcutaneously or intramuscularly, once or twice weekly. In artificially induced climacteric a daily oral dosage of 0.5 to 1.5 mg. may be necessary. For palliation of mammary cancer, 15 mg. is the daily oral dosage.

THE BIO-RAMO DRUG COMPANY

Tablets Dienestrol: 0.1, 0.5 and 1.5 mg.

THE CENTRAL PHARMACAL COMPANY

Suspension Restrol: 10 cc vials. A suspension containing 5 mg. of dienestrol in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Tablets Restrol: 0.1 and 0.5 mg.

VICTOR M. HERMELIN AND COMPANY, NEW PRODUCTS DIVISION OF KEITH-VICTOR PHARMACAL COMPANY

Tablets Dienestrol: 0.5 mg.

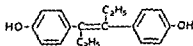
LLOYD & DABNEY COMPANY, INC.

Tablets Dienestrol: 0.1, 0.25, 0.5 and 5 mg.

WHITE LABORATORIES, INC.

Tablets Dienestrol: 0.1, 0.5 and 10 mg.

DIETHYLSTILBESTROL-U.S.P.—*Stilbestrol*.— α,α' -Diethyl-4,4'-stilbenediol.—“Diethylstilbestrol, dried at 105° for 2 hours, contains not less than 98.5 per cent of $C_{18}H_{20}O_2$ ” U. S. P. The structural formula of diethylstilbestrol may be represented as follows:



Physical Properties.—Diethylstilbestrol is a white, odorless, crystalline powder, melting between 169 and 172°. It is almost insoluble in water but is soluble in alcohol, fat solvents and fatty oils and in dilute alkali hydroxides. It should be stored in tight, light-resistant containers.

Actions and Uses.—Dodds and his co-workers, after extensive experimentation with synthetic substances, recognized the estrogenic activity of the stilbene compounds. Diethylstilbestrol is the most potent of these products described up to the present time.

It may be prepared in a variety of ways from nonbiologic, organic chemicals. Its physiologic activity duplicates practically all the known actions of natural estrogens. Thus it induces estrus in rodents, stimulates the growth of the endometrium and myometrium, primes the endometrium for progestational changes, causes reddening of the "sex skin" of monkeys and feminization of the plumage of birds, induces growth of mammary ducts in female and male animals as well as in human beings, raises the blood fat and calcium in fowl, induces withdrawal uterine bleeding in castrated animals and human beings and suppresses ovulation. It also inhibits the secretion of various factors of the anterior pituitary gland in experimental animals. It differs in its action from natural estrogens in its inability to cause the ovipositor reaction of the female bitterling and to antagonize the action of testosterone in the comb growth of capons. It has been used for the treatment of various conditions in human beings.

Dosage.—The average therapeutic dose for the treatment of menopausal symptoms is 0.5 to 1 mg. daily by mouth, although it is advisable to start with smaller doses for patients who tend to develop disagreeable symptoms. In other conditions, courses of therapy a few weeks apart are recommended by some authorities. Injection of similar quantities of diethylstilbestrol in oil solution are administered one or more times weekly. Ointment or suppositories containing this material may be used for topical applications in the treatment of vulvar and vaginal conditions. In prostatic carcinoma, the recommended dosage is 3 mg. daily intramuscularly for several weeks if oral administration is not feasible, after which the dosage is reduced gradually to 1 mg. daily, or 0.5 mg. three times daily by mouth. For palliation of mammary cancer, 15 mg. is the daily oral dose recommended.

For uses and contraindications see the general statement on estrogen.

Dosage.—The average therapeutic dose for the treatment of menopausal symptoms is 0.5 to 1 mg. daily by mouth, although it is advisable to start with smaller doses for patients who tend to develop disagreeable symptoms. In other conditions, courses of therapy a few weeks apart are recommended by some authorities. Injection of similar quantities of diethylstilbestrol in oil solution are administered one or more times weekly. Ointment or suppositories containing this material may be used for topical applications in the treatment of vulvar and vaginal conditions. In prostatic carcinoma, the recommended dosage is 3 mg. daily intramuscularly for several weeks if oral administration is not feasible, after which the dosage is reduced gradually to 1 mg. daily, or 0.5 mg. three times daily by mouth. For palliation of mammary cancer, 15 mg. is the daily oral dose recommended.

ABBOTT LABORATORIES

Tablets Diethylstilbestrol: 0.5, 1 and 5 mg.

Vaginal Suppositories Diethylstilbestrol. 0.5 mg.

AMERICAN PHARMACEUTICAL COMPANY, INC.

Tablets Diethylstilbestrol: 1 and 5 mg.

BIO-INTRASOL LABORATORIES, INC.

Solution Diethylstilbestrol in Oil: 1 cc. ampuls. A solution in sesame oil containing 1 mg. of diethylstilbestrol in each cubic centimeter.

THE BOWMAN BROS. DRUG COMPANY

Tablets Diethylstilbestrol: 5 mg.

BOYLE & COMPANY

Tablets Diethylstilbestrol: 5 mg.

CHICAGO PHARMACAL COMPANY

Tablets Diethylstilbestrol: 1 and 5 mg., uncoated; 0.25, 0.5, 1 and 5 mg., sugar coated.

COLE CHEMICAL COMPANY

Tablets Diethylstilbestrol: 1 mg.

THE DRUG PRODUCTS COMPANY, INC.

Pulvoids Diethylstilbestrol: 0.1 and 1 mg.

ENDO PRODUCTS, INC.

Solution Diethylstilbestrol in Oil: 1 cc. ampuls. A solution in sesame oil containing 0.5, 1, 2 and 5 mg. of diethylstilbestrol in each cubic centimeter.

ESTRO CHEMICAL COMPANY, INC.

Solution Diethylstilbestrol in Oil: 1 cc. ampuls and 30 cc. vials. A solution in corn oil containing 1, 2 and 5 mg. of diethylstilbestrol in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

THE EVRON COMPANY, INC.

Tablets Diethylstilbestrol: 1 and 5 mg.

GOLD LEAF PHARMACAL COMPANY, INC.

Solution Diethylstilbestrol in Oil: 1 cc. ampuls and 30 cc. vials. A solution in sesame oil containing 1 and 5 mg. of diethylstilbestrol in each cubic centimeter. The vials are preserved with 0.5 per cent chlorobutanol.

KEITH-VICTOR PHARMACAL COMPANY

Tablets Diethylstilbestrol: 1 and 5 mg.

ELI LILLY & COMPANY

Solution Diethylstilbestrol in Oil: 1 cc. ampuls. A solution in cottonseed oil containing 1 or 5 mg. of diethylstilbestrol in each cubic centimeter.

Suppositories Diethylstilbestrol: 0.1 and 0.5 mg.

Tablets Diethylstilbestrol: 0.1, 0.25, 0.5, 1 and 5 mg.

PAUL MANEY LABORATORIES, INC.

Tablets Diethylstilbestrol: 0.1, 0.25, 0.5, 1 and 5 mg.

E. S. MILLER LABORATORIES, INC.

Solution Diethylstilbestrol in Oil with Benzocaine 2%: 1 cc. ampuls. A solution in sesame oil containing 0.5 mg. of diethylstilbestrol in each cubic centimeter with 2 per cent benzocaine. Preserved with 0.5 per cent cresol.

Tablets Diethylstilbestrol: 0.1, 0.5 and 1 mg.

PHYSICIANS' DRUG AND SUPPLY COMPANY

Tablets Diethylstilbestrol. 0.2, 0.5, 1 and 5 mg.

PFENIO PHARMACEUTICAL LABORATORIES, INC.

Solution Diethylstilbestrol in Oil: 1 cc. ampuls. A solution in peanut oil containing 5 mg. of diethylstilbestrol in each cubic centimeter.

Tablets Diethylstilbestrol: 1 and 5 mg.

Vaginal Suppositories Diethylstilbestrol: 0.1 and 0.5 mg.

REXALL DRUG COMPANY

Tablets Diethylstilbestrol: 5 mg.

WILLIAM H. RORER, INC.

Tablets Diethylstilbestrol: 1 and 5 mg.

CARROLL DUNHAM SMITH PHARMACEUTICAL COMPANY

Tablets Diethylstilbestrol: 5 mg.

THE UPJOHN COMPANY

Perles Diethylstilbestrol: 0.1, 0.25, 0.5, 1 and 5 mg.

Solution Diethylstilbestrol in Oil: 1 cc. ampuls. A solution in cottonseed oil containing 1 mg. of diethylstilbestrol in each cubic centimeter.

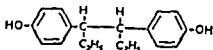
THE VALE CHEMICAL COMPANY, INC.

Tablets Diethylstilbestrol: 0.1, 0.5 and 1 mg.

WINTHROP-STEARN, INC.

Tablets Diethylstilbestrol: 5 mg.

HEXESTROL-N F. — *p,p'*-(1,2-Diethylethylene)diphenol. — *meso*-3,4-Di-*p*-hydroxyphenyl-*n*-hexane — "Hexestrol, dried at 105° for 4 hours, contains not less than 98.5 per cent of C₁₈H₂₂O₂" N.F. The structural formula of hexestrol may be represented as follows:



Physical Properties.—Hexestrol is an odorless, white, crystalline powder which melts between 185 and 188°. It is freely soluble in ether; soluble in acetone, alcohol and methanol; slightly soluble in benzene, carbon tetrachloride, chloroform, carbon disulfide, insoluble in water and in fixed oils and in dilute alcohol, hexestrol forms thin, platelike crystals of irregular, serrated outline.

Actions and Uses.—Hexestrol is used for the same conditions for which estrogenic substances are employed and the contraindications are those for natural estrogens. See the general statement on estrogen. Incidence of toxic symptoms is lower than that following

and then 0.2 to 1 mg. daily as a maintenance dose; or by injection, 1 mg. in oil three times weekly with similar lowering for maintenance of control. For senile vaginitis and kraurosis vulvae, 2 to 3 mg. daily by mouth, or 1 mg. in oil three times weekly by injection.

S. E. MASSENGILL COMPANY

Tablets Hexestrol: 3 mg.

THE Wm. S. MERRELL COMPANY

Solution Hexestrol in Oil: 20 cc. vials. A solution in vegetable oil containing 1 or 5 mg. of hexestrol in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

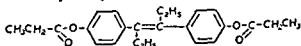
Tablets Hexestrol: 1 and 3 mg.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Hexestrol: 1 and 3 mg.

Esterified Stilbene Derivatives

DIETHYLSTILBESTROL DIPROPIONATE.— α,α' -Diethyl-4,4'-stilbenediol dipropionate.—The structural formula of diethylstilbestrol dipropionate may be represented as follows.



Physical Properties.—Diethylstilbestrol dipropionate is an odorless, tasteless, white, crystalline powder which melts between 105

and 107°. It is readily soluble in acetone, hot alcohol, benzene, chloroform, ether and hot methanol; soluble in vegetable oils.

same conditions for which estrogenic substances are employed, although when the drugs are administered intramuscularly in oil, reactions such as nausea and vomiting are less frequent with a dipropionate salt than with free diethylstilbestrol. Diethylstilbestrol dipropionate is absorbed relatively slowly from the oil depot and causes a lower blood stream concentration, although one of longer duration.

Dosage.—Diethylstilbestrol dipropionate in oil is administered intramuscularly, with the ratio of potency between oral and parenteral administration varying from 1:2 to 1:5. The following average dosages should be modified to meet individual requirements.

Menopause } from 0.5 to 2 mg. intramuscularly two or three
Senile vaginitis } times a week

Relief of breast engorgement—5 mg. intramuscularly once or twice daily for 2 to 4 days

Carcinoma of the prostate—3 mg. intramuscularly each day for about 10 days

After relief of symptoms the dosage should be reduced until the minimum effective dose for maintenance has been established.

THE BLUE LINE CHEMICAL COMPANY

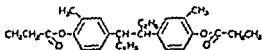
Solution Diethylstilbestrol Dipropionate in Oil: 10 cc. vials. A solution in peanut oil containing 1 or 5 mg. of diethylstilbestrol dipropionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Tablets Diethylstilbestrol Dipropionate: 1 and 5 mg.

CHEMO PURO MANUFACTURING CORPORATION

Powder Diethylstilbestrol Dipropionate: Bulk; for manufacturing use

PROMETHESTROL DIPROPIONATE.—Meprene Dipropionate (REED & CARNICK).—Dimethylhexestrol dipropionate.—4,4'-(1,2-diethylethylene)di-*o*-cresol dipropionate.—The structural formula of promethestrol dipropionate may be represented as follows:



Physical Properties.—Promethestrol dipropionate is a white, odorless, crystalline powder, which melts between 113 and 116°. It is freely soluble in benzene, ether and ethyl acetate, slightly soluble in alcohol and practically insoluble in dilute acids, dilute

alkalis and water. A solution of promethestrol dipropionate in 90 per cent alcohol is neutral to litmus.

Actions and Uses.—Promethestrol dipropionate is similar in its actions to diethylstilbestrol and other synthetic estrogens. See the general statement on estrogen.

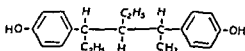
Dosage.—In the menopause, treatment may be started with 1 mg. given three times daily, gradually reducing the dosage to 1 mg. daily.

REED & CARRICK

Tablets Meprane Dipropionate: 1 mg.

Unclassified Derivatives of Nonsteroid Estrogens

BENZESTROL.—3-Ethyl-2,4-bis(*p*-hydroxyphenyl)hexane.—Benzestrol is one pair of racemates of the synthetic substance possessing the following structural formula.



Physical Properties.—Benzestrol is an odorless, white, crystalline powder which melts between 161 and 163°. It is readily soluble in acetone, alcohol, ether, methanol and sodium hydroxide T.S., soluble in vegetable oils, moderately soluble in glacial acetic acid, slightly soluble in dilute alcohol, benzene, chloroform and petroleum ether and practically insoluble in water and dilute mineral acids.

Actions and Uses.—See the general statement on estrogen. Incidence of toxicity is low with benzestrol.

Dosage.—By biologic assay, 1 mg of benzestrol is equivalent to approximately 25 mg of estrone. Average dosage for control of menopausal symptoms and senile vaginitis orally, 2 to 3 mg.; by injection, 2 to 5 mg. This may be repeated daily for 4 to 7 days until the dosage requirement is determined by clinical observation. For relief of breast engorgement, 5 mg. orally, three or four times daily for 5 or 6 days may be given. For prostatic carcinoma, the recommended dosage is 5 to 15 mg. two or three times weekly by injection if oral administration is not feasible, after which the dosage is gradually reduced.

SCHIEFFELIN & COMPANY

Elixir Benzestrol: 473 cc bottles. A flavored elixir containing 0.5 mg. of benzestrol in each cubic centimeter.

Solution Benzestrol: 10 cc multiple dose vials. A solution containing 5 mg of benzestrol in each cubic centimeter.

Suspension Benzestrol with Benzyl Alcohol 2%: 1 cc. ampuls and 10 cc. vials. An aqueous suspension containing 5 mg. of benzestrol in each cubic centimeter.

Tablets Benzestrol: 0.5, 1, 2 and 5 mg.

Vaginal Tablets Benzestrol: 0.5 mg

U S patents 2,400,033 and 2,400,034.

Lututrin

LUTUTRIN.—Lutrexin (HYNSON, WESTCOTT & DUNNING).—A uterine relaxing factor obtained from the corpus luteum of sow ovaries by a process of salting out followed by dialysis. It is a protein or polypeptide. It is assayed biologically.

Actions and Uses.—Lututrin, a water-soluble, proteinlike factor obtained from the corpus luteum of the ovary, produces a potent relaxant effect on the guinea pig uterus. Its constitution is somewhat similar to relaxin (Hisaw), a term used to designate a luteal hormone that produces relaxation of the symphysis pubis in the guinea pig, however, lututrin, as assayed primarily for uterine relaxant effect, exhibits little uniformity in relaxin activity. The uterine relaxing factor is not destroyed in the stomach, since the active principle appears in the blood serum within 30 minutes after oral administration.

Lututrin is useful in the treatment of functional dysmenorrhea. In a considerable proportion of patients it relieves to varying degrees the entire symptom complex of that disorder but is not effective in those women with major psychosomatic difficulties or pelvic anatomic abnormalities. Its effectiveness is enhanced by early administration, ideally the day prior to the onset of menstruation, but certainly before menstrual cramping becomes severe or nausea occurs. Evidence is inadequate to justify its earlier use for the relief of premenstrual tension or for the treatment of threatened or habitual abortion and other conditions involving hypercontractility of the uterus.

Lututrin produces no sedative action, but large doses have been followed by some drowsiness. No other side effects have been observed with moderate doses.

Dosage.—Lututrin is administered orally. Dosage is expressed in terms of units of activity on the guinea pig uterus. A unit is defined as "the minimal amount of substance which, when injected intravenously into the estrogenized virgin guinea pig, effects a 90 per cent reduction in the height of spontaneous contractions for a period of at least 10 minutes."

For dysmenorrhea the usual effective dosage ranges from 2,000 to 4,000 units initially, preferably before onset of severe symptoms, followed by 2,000 to 3,000 units every 3 or 4 hours as required. Individual response varies, and doses as high as 10,000 units have been employed without untoward effects.

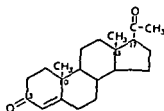
HYNSON, WESTCOTT & DUNNING, INC.

Tablets Lutrexin: 1,000 units of lututrin.

U S trademark 377,663.

Progesterone

PROGESTERONE-U.S.P.—Corlutone (GOLD LEAF).—4-Pregnene-3,20-dione.—The structural formula of progesterone may be represented as follows.



Physical Properties.—Progesterone occurs as a white, crystalline powder. It is colorless and is stable in air. Progesterone is practically insoluble in water; it is soluble in alcohol, in acetone and in dioxane. It is sparingly soluble in vegetable oils.

Actions and Uses—Progesterone, originally obtained from the corpus luteum but now made synthetically, is of value in the treatment of functional uterine bleeding ("metropathia hemorrhagica"). Its use for the treatment of primary or secondary amenorrhea, with or without estrogen, is incompletely established. Although progesterone long has been employed in the treatment of threatened or habitual abortion, dysmenorrhea and menorrhagia, there is insufficient satisfactory evidence to establish its effectiveness for these conditions.

Dosage.—Progesterone is ineffective orally. It is administered either intramuscularly in oil solution or subcutaneously in aqueous suspension in doses up to 20 mg. daily.

THE BIO-INTRASOL LABORATORIES, INC.

Solution Progesterone in Oil with Benzyl Alcohol 2%: 10 cc. vials. A solution containing 10 or 25 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Aqueous Suspension Progesterone with Procaine Hydrochloride 1%: 10 cc. vials. An aqueous suspension containing 10 or 25 mg. of progesterone in each cubic centimeter. Preserved with thimerosal 1:10,000.

BIOPHYSICS LABORATORIES, INC.

Solution Progesterone in Oil with Benzyl Alcohol 2%: 10 cc. vials. A solution in sesame oil containing 25 mg. of progesterone in each cubic centimeter. Preserved with 0.004 per cent phenylmercuric benzoate.

CARLO ERBA, INC.

Solution Progesterone in Oil: 10 cc. vials. A solution in peanut oil containing 10 or 25 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

GOLD LEAF PHARMACAL COMPANY, INC.

Solution Corlutone in Oil: 1 cc ampuls and 10 cc. vials. A solution in sesame oil containing 10 and 25 mg. of progesterone in each cubic centimeter. The 10 cc. vials are preserved with 0.5 per cent chlorobutanol.

KREIERS-URBAN COMPANY

Solution Progesterone in Oil: 10 cc. vials. A solution in sesame oil containing 10 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Solution Progesterone in Oil with Benzyl Alcohol 5%: 10 cc. vials. A solution in sesame oil containing 25 mg. of progesterone in each cubic centimeter.

LINCOLN LABORATORIES, INC.

Solution Progesterone in Oil with Benzyl Alcohol 2%: 10 cc. vials. A solution in sesame oil containing 10 or 25 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Aqueous Suspension Progesterone: 10 cc. vials. A suspension containing 10 mg. of progesterone in each cubic centimeter of physiologic isotonic sodium chloride solution. Preserved with 1 per cent acacia and thimerosal 1:10,000.

MEYER CHEMICAL COMPANY

Solution Progesterone: 10 cc. vials. A solution in sesame oil containing 10 or 25 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

THE UPJOHN COMPANY

Solution Progesterone in Oil: 1 cc. ampuls and 5 cc. vials. A solution in cottonseed oil containing 5 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

5 cc. vials. A solution in cottonseed oil containing 10 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

10 cc. vials. A solution in cottonseed oil containing 25 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Aqueous Suspension Progesterone: 1 and 10 cc. vials. A suspension in isotonic salt solution containing 25 mg. of progesterone in each cubic centimeter. Preserved with thimerosal 1:10,000.

THE VETARINE COMPANY, INC.

Solution Progesterone in Oil: 1 cc. ampuls. A solution in sesame oil containing 5 or 10 mg. of progesterone in each cubic centimeter. **10 cc. vials.** A solution in sesame oil containing 10 mg. of progesterone in each cubic centimeter. Both sizes preserved with 0.5 per cent chlorobutanol.

Solution Progesterone in Oil with Benzyl Alcohol 3%: 10 cc. vials.

A solution in sesame oil containing 25 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

PANCREAS

The pancreas has two primary functions: (1) It secretes into the intestine a digestive juice containing the enzymes trypsin, lipase and amylase; (2) it secretes into the blood a hormone, insulin,

Diabetes is a disease characterized by hyperglycemia due to insulin deficiency or possibly to other causes. In this disease the percentage of sugar increases in the blood (hyperglycemia) so that sugar overflows into the urine (glycosuria). The hyperglycemia is associated with a breakdown of the first stage in the metabolism of sugar, as revealed by the deficient formation of glucose-6-phosphate and the consequent failure of glycogen deposition in the liver and the failure of the respiratory quotient to become increased when carbohydrate food is ingested. The depression in carbohydrate metabolism may be accompanied by an accumulation of ketone substances (acetone, acetoacetic and oxybutyric acids) with resultant acidosis and, later, coma.

Insulin

Insulin, if administered subcutaneously, intravenously or intraperitoneally, causes a fall in the sugar content of the blood. Insulin prevents the hyperglycemia due to piqure, asphyxia and epinephrine. It increases the sugar consumption of the isolated mammalian heart. Insulin also causes glycogen to be deposited in the liver and possibly in the muscles and raises the respiratory quotient of diabetic animals fed with carbohydrates. It affects the metabolism of fat in diabetic animals and causes the acetone bodies to disappear from the urine.

Insulin also acts as an antagonist to certain pituitary and adrenal hormones. When the percentage of blood sugar falls below the kidney threshold in the diabetic patient, sugar disappears from the urine. If an overdose of insulin is given, the blood sugar falls to a subnormal level, and characteristic symptoms are observed. The level at which these symptoms occur depends not only on the extent but also on the rate of fall. If the blood sugar has been persistently high and is reduced rapidly, hypoglycemic symptoms may appear at a much higher level of blood sugar than when the fall is slower and more gradual. These symptoms are due to the diminished sugar content of the blood, as shown by the fact that they are relieved by the replacement of the sugar by oral or intravenous administration.

Clinical assays conducted on patients with uncomplicated diabetes on certain standard dietary regimens reveal that one insulin unit promotes the metabolism of approximately 1.5 Gm. of dextrose.

The administration of insulin to diabetic dogs and to men with severe diabetes mellitus temporarily restores the impaired ability to oxidize carbohydrate and to store glycogen in the liver. If a suitable dose of insulin is administered at regular intervals to a person suffering from diabetes mellitus, the blood sugar is maintained at a normal level, the urine remains free of sugar and there

suria and good mental and physical vigor for patients with severe diabetes

Administration of insulin is indicated in cases of diabetes mellitus that cannot be controlled at a satisfactory level by dietetic treatment. In such cases, the diet should be weighed carefully, be of known composition and insulin administered in such amounts as to prevent glycosuria and excessive hyperglycemia. In some cases the dosage of insulin may be decreased gradually as the body's capacity for utilizing carbohydrate returns toward normal.

regulation and exercise alone may produce improvement.

the pancreatic
d. Pancreatin-
to value in the
- after pancreat-
lack of or de-
ficient external secretion of the pancreas. It is standardized to convert not less than 25 times its weight of potato starch or casein into soluble carbohydrates and proteoses, respectively

Overdosage.—Overdosage of insulin produces serious symptoms which demand immediate treatment. The patient complains of weakness, fatigue and nervousness or tremulousness, followed by profuse sweating, the most characteristic sign of overdosage, and sometimes pallor or flushing. In severe forms there is acute distress with mental disturbances and even unconsciousness. These symptoms are relieved by the administration of some form of soluble carbohydrate, such as orange juice, by mouth or stomach tube, or, if the patient is comatose, by the intravenous injection of 5 to 20 Gm. of pure dextrose in a 5 to 50 per cent sterile solution.

mouth. The injection of epinephrine must be employed carefully as its action depends on the presence of glycogen, of which there usually is very little in the diabetic organism. Epinephrine should never be employed when the hypoglycemia follows excessive exercise, vomiting or the omission of meals.

Insulin has been used in the treatment of nondiabetic malnutrition with reported increase in appetite and gain in weight. Care

fully qualified and thoroughly familiar with all aspects of this method of treatment. It is essential to have available at all times suitable solutions of dextrose for interrupting the hypoglycemic state that thus is created artificially.

Dosage.—Insulin is administered by injection into the loose subcutaneous tissue of the body, usually 30 minutes before meals. There is no average dose of insulin for diabetics; each case must be studied individually. Except when complications occur insulin is not indicated when a patient has adequate dextrose tolerance to provide him with a diet sufficient for light work. In mild diabetes, a single dose of insulin usually is given before breakfast. If glycosuria is not controlled in this way, a smaller dose may be given before supper. When more than one dose is required daily, usually it is better to use one of the long-acting insulin preparations. Less carbohydrate should be given at breakfast than at the other two meals. When the patient becomes aglycosuric the diet usually may be increased. Sufficient insulin should be used to keep the fasting blood sugar normal, but hypoglycemia should be avoided. If patients are not under close observation, half the estimated dose may be used and the dose increased gradually until therapeutic results are obtained. Complications, such as infections, may reduce the dextrose tolerance, thus necessitating an increase of insulin dosage.

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Dosage of insulin always should be expressed in units rather than in cubic centimeters or minims. The volume of a dose of insulin

containing a certain number of units will vary with the strength of the solution employed. It is advisable to keep the volume per injection at 0.25 to 0.75 cc., choosing the strength of insulin which will give the required number of units within this range.

Insulin injection prepared from zinc insulin crystals, globin insulin injection and protamine zinc insulin all are official in the U. S. Pharmacopeia. Unmodified insulin is the preparation of choice in the treatment of diabetes acidosis and coma and when the glucose tolerance is fluctuating rapidly, as in the presence of infection, shock or surgical trauma.

Canadian patents 334,336 and 234,337. U. S. trademark 179,174. Canadian trademark 31,646.

Insulin Labeling Regulations

Regulations concerning the certification of batches of drugs composed wholly or partly of insulin are presented in the 15 Federal Register 7359, Nov. 2, 1950, as amended by 16 F.R. 10157, Oct. 5, 1951 and 17 F.R. 1822, Feb. 29, 1952. Of special interest to the physician are statements on labeling. Each package must contain on the outside wrapper information on the batch mark, strength of the drug in terms of U.S.P. units of insulin per cubic centimeter, expiration date and the warning "Keep in a cold place. Avoid freezing." The circular or other labeling must contain special information for the guidance of the physician and patient. The outside containers or wrappers must be distinguished by various colors.

Insulin U.S.P. is distinguished by:

Red, if it contains 40 U.S.P. Units of insulin in each cubic centimeter.

Green, if it contains 80 U.S.P. Units of insulin in each cubic centimeter.

Orange, if it contains 100 U.S.P. Units of insulin in each cubic centimeter.

Narrow (at least 5 but not more than 20 to each inch) brown and white diagonal stripes, if it contains 500 U.S.P. Units of insulin per cubic centimeter.

If the master lot used was in crystalline form the distinguishing colors may be:

Red and gray, if it contains 40 U.S.P. Units of insulin in each cubic centimeter.

Green and gray, if it contains 80 U.S.P. Units of insulin in each cubic centimeter.

Protamine zinc insulin is distinguished by:

Red and white, if it contains 40 U.S.P. Units of insulin in each cubic centimeter.

Green and white, if it contains 80 U.S.P. Units of insulin in each cubic centimeter.

Globin zinc insulin is distinguished by:

Red and brown, if it contains 40 U.S.P. Units of insulin in each cubic centimeter.

Green and brown, if it contains 80 U.S.P. Units of insulin in each cubic centimeter.

Isophane (NPH) insulin is distinguished by:

Red and blue, if it contains 40 U.S.P. Units of insulin in each cubic centimeter.

Green and blue, if it contains 80 U.S.P. Units of insulin in each cubic centimeter.

ZINC INSULIN CRYSTALS.—A crystalline preparation of the active antidiabetic principle of the internal secretion of the islands of Langerhans of the pancreas. The crystals contain a small amount of zinc (not less than 0.45 per cent and not more than 0.9 per cent), which is combined chemically with the active principle. Each milligram of the crystals is equivalent to not less than 22 units of insulin. The product is marketed in the form of a solution for injection.

Marketed solutions of zinc insulin crystals are water clear and contain from 1.4 to 1.8 per cent (w/v) of glycerin for isotonicity, 0.1 to 0.25 per cent (w/v) of phenol or cresol as a preservative and sufficient 0.01 *N* hydrochloric acid to yield a pH of 2.5 to 3.5. The biologic activity of the solution is expressed in U.S.P. Insulin Units per cubic centimeter. Solutions of zinc insulin crystals are stable, provided the storage temperature does not exceed room temperature.

Actions and Uses.—Zinc insulin crystals are used in the form of injectable solutions in the treatment of diabetes mellitus that is not controlled by diet. Ordinarily, crystalline preparations are interchangeable with amorphous preparations. However, because of their purity, solutions of zinc insulin crystals minimize the allergic reactions that sometimes occur with amorphous insulin. Crystalline solutions, therefore, are indicated for patients who may be expected to exhibit such reactions.

Dosage.—The potency of solutions of zinc insulin crystals is measured in terms of standard units of insulin. Like solutions of regular amorphous insulin, solutions of zinc insulin crystals usually are best administered subcutaneously 15 to 30 minutes before a meal. The time and number of doses and the amount of solution must be determined by the needs of the individual patient, each one requiring accurate dietary regulation and meticulous clinical study.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Insulin Made From Zinc Insulin Crystals: 10 cc. vials. Aqueous

solutions containing 40 or 80 units in each cubic centimeter. Preserved with 0.1 per cent of phenol

Long-Acting Insulin Preparations

Several preparations of insulin combined with globin or protamine are used to prolong the blood sugar lowering action of the hormone. These vary in their duration of action from 15 to 72 hours and characteristically possess a slower onset of action than

of the various forms of long-acting insulin and is presented as a guide. It should be noted, however, that patients may vary considerably in their reactions, each requiring meticulous clinical study to determine the onset, peak and duration of action of the preparation used.

	<i>Soluble Unmodified and Crystalline Zinc Insulin</i>	<i>Globin Insulin</i>	<i>Isophane Insulin</i>	<i>Protamine Zinc Insulin</i>
Onset	1 hr.	1 to 2 hrs.	1 to 2 hrs.	4 to 6 hrs.
Peak Action	2 to 3 hrs.	6 to 12 hrs.	10 to 20 hrs.	16 to 24 hrs.
Duration	6 to 8 hrs.	18 to 24 hrs.	20 to 32 hrs.	24 to 36 hrs. or longer

GLOBIN ZINC INSULIN.—GLOBIN ZINC INSULIN INJECTION—U.S.P.—Globin Insulin with Zinc—"Globin Zinc Insulin

certification of drugs composed wholly or partly of insulin.

"In the preparation of Globin Zinc Insulin Injection, the amount of insulin used is sufficient to provide either 40 or 80 U.S.P. Insulin Units for each ml. of the Injection.

"Globin Zinc Insulin Injection differs in its action from that of other insulin injections both in time of onset and duration." U.S.P.

Physical Properties.—Globin zinc insulin injection is an almost colorless liquid, substantially free from turbidity and insoluble matter. Globin zinc insulin injection contains from 1.3 to 1.7 per cent (w/v) of glycerin and either 0.15 to 0.2 per cent (w/v) of cresol or 0.2 to 0.26 per cent (w/v) of phenol. It contains 0.25 to 0.33 mg. of zinc for each 100 U.S.P. Units. It also contains

3.6 to 4 mg. of globin (calculated as six times the nitrogen content of the globin) for each 100 U.S.P. Insulin Units.

Actions and Uses.—The effects of globin insulin with zinc are essentially the same as those of insulin except that the action is intermediate between that following regular insulin and protamine zinc insulin. The period of greatest effect extends from the eighth to the sixteenth hour after injection; it almost disappears at the end

adequate control and in some patients to replace, wholly or partly, ordinary insulin. It is indicated for patients who require more than one daily injection of unmodified insulin and for those whose sugar level cannot be controlled by other forms of insulin or who exhibit sensitivity to protamine. Its injection also produces fewer local reactions. It is not recommended for the treatment of diabetic coma and never should be administered intravenously. Globin insulin with zinc is stable but nevertheless bears on the label an expiration date for usage.

Dosage.—For general principles underlying the administration of this form of insulin see the general statement on insulin. Globin zinc insulin must be administered only by deep subcutaneous injection, not intramuscularly or intravenously. Dosage must be determined by a study of the patient. The initial dose may be about two-thirds to three-fourths of the total daily dose of regular insulin. This may be increased slowly as needed. If the patient has been receiving protamine zinc insulin, the globin insulin dosage on the first day should not exceed one-half the total dose of all insulin (regular, protamine zinc) received on the previous day. On the next day the dose may be increased to two-thirds of the previous total insulin dosage and then slowly adjusted.

BURROUGHS WELLCOME & COMPANY, INC.

Globin Insulin with Zinc: 10 cc. vials. A sterile solution in hydrochloric acid of 40 or 80 U.S.P. Insulin Units in each cubic centimeter. Preserved with 0.25 per cent phenol

U. S. patent 2,161,198

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Globin Zinc Insulin. 10 cc. vials. A sterile solution in hydrochloric acid of 40 or 80 U.S.P. Insulin Units in each cubic centimeter. Preserved with 0.25 per cent phenol

ISOPHANE INSULIN.—ISOPHANE INSULIN INJECTION.—U.S.P.—NPH Insulin (Lilly)—NPH Insulin—"Isophane Insulin Injection is a sterile suspension, in a buffered water medium, of the addition of the suspension, and zinc. The mature testes, kley, or *Salmo* regulations of the

federal Food and Drug Administration concerning certification of drugs composed wholly or partly of insulin.

"In preparing Isophane Insulin Injection, sufficient insulin is used to provide either 40 or 80 U.S.P. Insulin Units for each ml. of the Injection.

"Isophane Insulin Injection differs in its action from other insulin injections."

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The pharmacologic action of isophane insulin is similar to that of the other insulins. Its blood sugar lowering action places it in an intermediate position between globin insulin and protamine zinc insulin. The onset of action for isophane insulin begins usually 2 hours after subcutaneous injection, whereas 6 to 8 hours are required for protamine zinc insulin. Its peak effect occurs 10 to 20 hours after administration, and its duration of action is 28 to 30 hours.

Isophane insulin may be mixed with regular insulin. Loss of quick action of regular insulin is less with isophane insulin than with similar mixtures of protamine zinc insulin.

Isophane insulin is not recommended for children under 5 years of age or for patients who require quick-acting insulin.

Dosage.—See the monograph on protamine zinc insulin.

Warning.—If administered after breakfast, danger of nocturnal hypoglycemia exists.

ELI LILLY & COMPANY

NPH Insulin: 10 cc vials 40 or 80 units in each cubic centimeter. Preserved with 0.15 per cent *m*-cresol and 0.06 per cent phenol.

E. R. SQUIER & SONS, DIVISION OF OLIN MATTHEWSON CHEMICAL CORPORATION

NPH Insulin: 10 cc vials 40 or 80 units in each cubic centimeter. Preserved with 0.15 per cent *m*-cresol and 0.06 per cent phenol.

U. S. patent 2,538,018

LENTE INSULIN.—Lente Insulin (Lilly).—"Lente insulin is a sterile suspension, in a buffered water medium, of insulin modified by the addition of zinc chloride. Of the insulin contained in the preparation not more than 1 U.S.P. Unit of insulin per milliliter is in solution, approximately 70 per cent is crystalline, and the remainder is amorphous. Zinc-insulin crystals are used in such quantity that each milliliter of the preparation, when the precipitate therein is brought into uniform suspension, contains either 40 or 80 U.S.P. Units of insulin. The preparation contains, for each 100 U.S.P. Units of insulin, not less than 0.20 milligram and not more than 0.35 milligram zinc (of which not less than 40 per cent nor more than 65 per cent is in the supernatant liquid), and not more than 0.65 milligram nitrogen. The preparation also con-

tains not less than 0.15 per cent and not more than 0.17 per cent (w/v) sodium acetate, not less than 0.65 per cent and not more than 0.75 per cent (w/v) sodium chloride, and not less than 0.09 per cent and not more than 0.11 per cent (w/v) methyl-*p*-hydroxybenzoate. The pH of the finished product is not less than 7.1 nor more than 7.5." Certification of Batches of Drugs Composed Wholly or Partly of Insulin [19 Fed. Reg. 4153 (July 8, 1954)].

Actions and Uses.—Lente insulin is a mixture of minute particles consisting of approximately 70 per cent crystalline zinc insulin and 30 per cent amorphous zinc insulin, each component of which has a sufficiently high zinc content to make the mixture relatively insoluble at the pH of the blood. The proportion of the components provides an antidiabetic action that is intermediate in time between that of unmodified (regular) insulin and protamine zinc insulin. The time of action of lente insulin so closely approximates that of the modified protamine zinc insulin, isophane (NPH) insulin, that they can be used interchangeably. The onset of action

sensitivity reactions attributed to protamine or globin. Since lente insulin differs clinically from unmodified insulin only in its more prolonged action in lowering the blood sugar, its administration and dosage should follow the same principles that govern the use of insulin in general; however, lente insulin is not adaptable for use in place of unmodified insulin in dealing with diabetic emergencies that require immediate-acting intravenous insulin. Also see the general statement on insulin.

Dosage.—Lente insulin is administered as a buffered suspension by deep subcutaneous injection. It should not be injected into underlying muscle and is *never administered intravenously*. The container vial should be rotated and inverted several times to insure uniform distribution of the suspended particles, but vigorous shaking and frothing should be avoided. The potency is expressed in terms of insulin units per cubic centimeter of suspension. The number and size of daily doses, time of administration, diet, and exercise must be determined by careful observation under laboratory control, with frequent blood sugar estimations and urinary sugar examinations in each individual case. Usually the most satisfactory time for injection is in the morning before breakfast. In newly developed uncomplicated cases of average severity, an initial daily dose of 10 units may be administered before breakfast; then this may be increased by 3 to 5 units until proper control of blood and urinary sugar is achieved. In patients already under treatment with protamine zinc insulin or unmodified insulin or both, a beginning dose of lente insulin of approximately 20 per cent fewer units may be substituted; this is increased if necessary. Patients on isophane insulin may be transferred directly to lente insulin on a unit-for-unit basis. In certain severe cases, further

regulation of diet may be important to obtain the optimum blood sugar level . . . of for . . . three . . . may . . . discretion of the physician

Suspensions of lente insulin should be stored in a cold place, preferably a refrigerator. Exposure to freezing or high temperatures should be avoided. Vials in use also should be protected from strong light and the contents used as continuously as possible. A partially empty vial not used for several weeks should be discarded. A vial in which the precipitated suspension has become clumped or deposited on the wall of the container should not be used.

ELI LILLY & COMPANY

Lente Insulin: 10 cc vials 40 or 80 units in each cubic centimeter
Preserved with 0.1 per cent methylparaben

PROTAMINE ZINC INSULIN—PROTAMINE ZINC INSULIN INJECTION—U.S.P.—Protamine Zinc and Insulin (Lilly)—“Protamine Zinc Insulin Injection is a sterile suspension, in a buffered water medium, of insulin modified by the addition of zinc chloride and protamine. The protamine is prepared from the sperm or from the mature testes of fish belonging to the genus *Oncorhynchus* Suckley, or *Salmo* Linné (Fam. *Salmonidae*), and conforms to the regulations of the federal Food and Drug Administration concerning certification of drugs composed wholly or partly of insulin.

“In the preparation of Protamine Zinc Insulin Injection, the amount of insulin used is sufficient to provide either 40 or 80 U.S.P. Insulin Units for each ml. of the Injection.

“Protamine Zinc Insulin Injection differs in its action from that of other insulin injections both in time of onset and duration.”
U.S.P.

Physical Properties.—Protamine zinc insulin injection is a white suspension and is freed of large particles when agitated moderately.

Actions and Uses.—The effects of protamine zinc insulin are the same as those of insulin (see general statement on insulin), except that unmodified insulin lowers blood sugar maximally in 2 to 3 hours, whereas the action of protamine zinc insulin in lowering blood sugar is prolonged and the agent is most effective 12 to 24 hours after administration.

Protamine zinc insulin may be used in any patient in whom regulation of diet is incapable of removing the cardinal objective symptoms of diabetes mellitus, and may replace, wholly or partly, the use of unmodified insulin. Unmodified insulin alone, protamine zinc insulin alone or both preparations give best results in different cases.

Because of the prolonged action of protamine zinc insulin, it is useful chiefly in cases where unmodified insulin does not provide control unless administered several times daily or where it is un-

able to provide adequate control unaccompanied by frequent hypoglycemic reactions, ketosis or pronounced fluctuations in blood sugar levels and when insulins of intermediate duration of action also are unsatisfactory. The use of protamine zinc insulin in patients in diabetic coma, in diabetes complicated by infection, or in the event of surgical operations is not recommended.

Dosage.—For the general principles underlying the administration of protamine zinc insulin see the general statement on insulin.

Protamine zinc insulin is to be injected *only subcutaneously*. In most cases its administration is not required more than once a day. The initial dose should be from about two-thirds to the same number of units that would be needed with unmodified insulin. Owing to the slow absorption and consequent delayed action of protamine zinc insulin, glycosuria may follow. Hence on the first few days when protamine zinc insulin is being used, it may be advantageous to administer a separate dose of unmodified insulin. Usually it is possible to discontinue the use of unmodified insulin after the first or second day, although in some instances the administration of both preparations must be continued indefinitely.

Protamine zinc insulin is administered in the morning (from $\frac{1}{2}$ to $1\frac{1}{2}$ hours before breakfast). Because protamine zinc insulin lowers the blood sugar level over a prolonged period, diet must be adjusted, and a redistribution of food among individual meals usually is desirable. The carbohydrate content of the meal following the injection of protamine zinc insulin may have to be limited to avoid hyperglycemia. The carbohydrate not included in this meal is divided between the other meals of the day, often including a night feeding, in such a manner as to prevent hypoglycemia at times when the dose of protamine zinc insulin is exerting its greatest effect.

Symptoms of hypoglycemic reactions following administration of protamine zinc insulin are similar to but may be less obvious than those

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patient may appear to be restored to normal through use of a soluble carbohydrate food such as orange juice, it is advisable to provide additional carbohydrate such as soda biscuits and milk after 1 or 2 hours. In severe reactions, it may be desirable to inject intravenously 15 to 20 Gm. of dextrose in sterile solution, giving food later.

ELI LILLY & COMPANY

Suspension Protamine Zinc and Iletin: 10 cc. vials. A buffered suspension containing 40 or 80 U.S.P. Insulin Units in each cubic centimeter.

Iletin is registered under U. S. trademark 171,971.

SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Suspension Protamine Zinc Insulin: 10 cc. vials. A buffered suspension containing 40 or 80 U.S.P. Insulin Units in each cubic centimeter. Preserved with 0.25 per cent phenol.

U. S. patents 2,076,082, 2,143,590 and 2,143,591.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Suspension Protamine Zinc Insulin: 10 cc vials. A buffered suspension containing 40 or 80 U.S.P. Insulin Units in each cubic centimeter.

U. S. patent 2,179,384.

PITUITARY GLAND

Anterior Lobe.—The anterior lobe apparently is not necessary for life, but its removal causes a marked decrease in the growth of the animal and a general loss of spontaneous activity. Such animals respond poorly to the usual measures for dealing with infections.

and a general loss of spontaneous activity. Such animals respond poorly to the usual measures for dealing with infections.

cells) containing acidophilic granules after staining, constituting about 35 per cent of the total mass and (3) basophilic cells (beta cells).

Although a large number of active substances in extracts and preparations of the anterior lobe have been described, many are probably not distinct compounds. How many distinct hormones are secreted by the gland is unknown, but at least seven extracts having highly specific action have been prepared in a relatively pure state. These are (1) A growth factor which influences the development of the body, (2) a factor (follicle-stimulating hormone, FSH) which stimulates the growth and maturation of the ovary in the female, which in some beings is the phenol phosphate

produces hyperplasia of the thyroid with hyperthyroidism in both the rat and the guinea pig; (5) a factor which produces growth

cells of the islets of Langerhans, thus producing the diabetic syn-

drome; (7) the adrenocorticotrophic hormone (corticotropin, ACTH), a factor which stimulates the adrenal cortex.

The gonadotropic hormones also are necessary for sexual development in the male, although the roles of FSH and LH are not clear. The growth hormone is believed to be derived from the acidophilic cells of the gland. The cellular source of the other factors is uncertain.

While several of these factors are in use in clinical studies, only corticotropin (ACTH) and gonadotropin are commercially available at the present time.

The Council believes that extensive clinical trial has failed to establish the value of desiccated pituitary preparations for oral administration whether these are prepared from the anterior or from the posterior lobe.

Posterior Lobe—Suitable extracts of the posterior lobe of the pituitary gland yield two active principles that are responsible for the principal pharmacological effects. These principles, oxytocin and vasopressin, have been isolated in pure form as octapeptides and their structural formulas are known, however, commercially available extracts represent either simple extracts containing both principles or refined extracts containing chiefly either oxytocin or vasopressin. The important effects of the extracts are on the smooth muscle of structures such as the uterus, the blood vessels, the intestines and the gall bladder and on the renal tubular epithelium. Although the peptides closely resemble each other in structure, their effects on the organs mentioned above differ considerably.

The important action of vasopressin is on the renal tubular epithelium where the hormone greatly accelerates the rate of reabsorption of water, especially during diuresis. Vasopressin appears not to have striking effects on electrolyte excretion by the kidney, provided that excessive doses are not used. Its antidiuretic action depends entirely upon this facilitation of the renal reabsorption of water and is not the result of a delayed absorption of water from the gastro-intestinal tract. Vasopressin used in larger doses will cause a stimulation of the smooth muscle of the blood vessels and the intestines. It is not useful as a vasopressor agent because of the danger of coronary vasoconstriction and consequent damage to the heart and because the response to repeated doses may fall progressively if an acute tolerance develops. Vasopressin also is an oxytocic agent and actually may be more potent than oxytocin itself at times other than during parturition, however, its use as an oxytocic agent is undesirable because of the possibility that injudicious doses may cause coronary vasoconstriction.

The other active principle, oxytocin, has two important actions. It strongly stimulates the specialized myoepithelium which is associated closely with the secreting epithelium of the lactating mammary gland. Thus, it is responsible for the ejection or "let-down" of milk that occurs in nursing when the hormone is released by reflex stimulation. Oxytocin has been used to facilitate nursing by mothers whose lactation appears to be normal. It has no effect on the secretion of milk. The other important action of oxytocin is on the uterus, especially late in pregnancy or during parturition.

It is a much more desirable oxytocic agent than vasopressin because it does not affect the coronary blood flow.

Posterior pituitary preparations are inactivated by enzymes of the gastro-intestinal tract and must be administered parenterally, although a rather inefficient absorption may occur after the extract or powdered gland has been applied to the nasal mucous membrane. Extracts may be given either subcutaneously or intramuscularly. Their use intravenously is a dangerous procedure which should be reserved for very dilute solutions administered at a slow rate under carefully controlled conditions.

Either oxytocin solution or whole pituitary extract is used in obstetrics to combat uterine atony and to lessen postpartum or other uterine hemorrhage. They should not be given during the first stage of labor because, with incomplete cervical dilatation, there is danger of uterine rupture or laceration of the cervix or other tissues. Most authorities advise against their use in the second stage of labor.

Vasopressin is the ideal therapeutic for the treatment of diabetes insipidus in which it offers complete replacement therapy by greatly increasing the renal reabsorption of water and thus reducing the volume of urine. A solution of vasopressin or vasopressin tannate in oil injected intramuscularly has been used for this purpose. Small intramuscular doses of vasopressin tannate in oil may not be required oftener than every 48 hours. Either vasopressin or posterior pituitary extract has been used to stimulate the smooth muscle in intestinal paresis. Doses must be relatively large, and the possibility of an associated coronary vasoconstriction always should be considered.

The *U. S. Pharmacopeia* includes Posterior Pituitary Injection, containing both oxytocin and vasopressin, and Oxytocin Injection, containing chiefly oxytocin. The usual intramuscular dose of the former is 0.3 to 0.5 cc. and of the latter 0.5 cc. The *U. S. Pharmacopeia* also includes Vasopressin Injection.

CORTICOTROPIN—CORTICOTROPIN INJECTION—U.S.P.—

Aether (Axiolux)—ACTH Injection—Adrenocorticotrophin Injection—Corticotrophin Injection—"Corticotropin Injection is a sterile preparation of the principle or principles derived from the anterior lobe of the pituitary gland of mammals used for food by man, which exert a tropic influence on the adrenal cortex. It possesses a potency of not less than 80 per cent and not more than 125 per cent of that stated on the label in U.S.P. Corticotropin Units. It may contain a suitable antibacterial agent." *U.S.P.*

Actions and Uses.—The adrenocorticotrophic hormone of the anterior pituitary gland stimulates the adrenal cortex to secrete its entire spectrum of hormones. Experimental evidence suggests that Compound F (hydrocortisone) is the chief component in the adrenocortical secretion although considerable quantities of cortisone and corticosterone are elaborated. Hormonal effect can be exerted only if a functioning adrenal cortex is present. Corticotropin is utilized rapidly in the body, its effect rarely exceeds 6 hours. This necessitates repeated intramuscular administration of

the drug or use of a slowly absorbed preparation. Corticotropin also may be administered intravenously by slow continuous drip over 8 hours; its effect usually persists for approximately 24 hours. The physiologic and metabolic effects of the hormone are due to the adrenal corticosteroids elaborated and are, in general, similar to those described for cortisone acetate. Because of its rapid absorption and utilization these effects appear more promptly than with parenteral or oral administration of cortisone acetate. The prompt fall of the circulating eosinophil count when therapeutic doses of corticotropin are given is the basis for the Thorn test of adrenocortical response. The drug is of value in the same disease conditions for which cortisone acetate is used except that it is not effective for the treatment of Addison's disease.

In general, long term administration of either corticotropin or cortisone acetate induces similar undesired hormonal effects. However, hypertension and hirsutism are more likely with the use of corticotropin, while cortisone acetate may elicit involution or partial atrophy of the adrenal cortex. A period of depressed adrenocortical function may follow sudden cessation of corticotropin administration.

The potent metabolic effects of corticotropin require frequent check on the patient's weight, blood pressure and electrolyte balance. A high potassium, low sodium intake is advisable if protracted treatment or a large dose of corticotropin is necessary.

With intravenous administration of corticotropin certain additional precautions are necessary. Patients known to be sensitive to animal extracts should have suitable intracutaneous tests with the brand of corticotropin to be used. If such tests are positive, it is preferable to use corticotropin from another animal source. Potassium intake of 2 to 5 Gm. daily should be assured, otherwise the reactions are the same as observed with intramuscular injection. Therapeutic response, however, is more prompt and in some instances patients refractory to intramuscular injection have responded following intravenous administration.

Corticotropin is contraindicated for long-term treatment in hypertension, diabetes mellitus, mental disturbances, chronic nephritis, and tuberculosis. It has been reported to cause hypokalemia and to increase the excretion of sodium and water.

Dosage.—The average adult dose of corticotropin is 40 to 50 U.S.P. units daily, administered intramuscularly in four divided doses. The dosage may be increased to 100 to 150 U.S.P. units daily in severe cases.

Intravenous administration by continuous drip apparently is more efficient in eliciting response and, therefore, requires lower dosage schedules. For intravenous use, 5 to 20 U.S.P. units are dissolved in 500 cc. of 5 per cent glucose in water or in 500 cc. of normal saline solution and administered slowly over an 8-hour

period. *Caution: Normal saline should not be used as the diluent if the patient is on a low salt regimen.*

THE ARMOUR LABORATORIES

Lyophilized Acthar (Pork): Vials containing the equivalent of 10, 15, 25 and 40 provisional U.S.P. units of corticotropin

THE UPJOHN COMPANY

Lyophilized Corticotropin (Sheep): Vials containing the equivalent of 25 and 40 provisional U.S.P. units of corticotropin

THE WILSON LABORATORIES

Solution Corticotropin: 5 cc. vials. A solution containing the equivalent of 40 U.S.P. units of corticotropin in each cubic centimeter. Preserved with 0.5 per cent phenol.

PURIFIED CORTICOTROPIN—Purified corticotropin is prepared by the adsorption of corticotropin from a dilute acetic acid solution on oxycellulose and the subsequent elution of the adsorbed material with dilute hydrochloric acid. This method yields a product having 10 to 40 times the adrenocorticotrophic activity of an equivalent weight of corticotropin.

Purified corticotropin is assayed biologically by measurement of the adrenal ascorbic acid depletion response in hypophysectomized rats. Comparison is made to the Provisional U.S.P. Corticotropin Reference Standard, the injections being made intravenously as with corticotropin. When injected subcutaneously or intramuscularly, however, purified corticotropin produces a greater clinical effect unit for unit than does corticotropin; thus 1 U.S.P. of purified corticotropin produces a clinical effect attained by 3 or 4 units of corticotropin. But when administered intravenously, one U.S.P. unit of purified corticotropin, as measured by rat assay, produces the same range of clinical response as one unit of corticotropin. The exact reason for this discrepancy in response is unknown. It has been hypothesized that the cruder corticotropin carries with it some factors which permit more rapid enzymatic destruction in muscle or skin. These factors are thought to be absent, or present in lesser quantity, in purified corticotropin. For the convenience of physicians, the potency of purified corticotropin is expressed in terms of clinical activity equivalent to a specified number of U.S.P. units of corticotropin, so that treatment may be changed from corticotropin to purified corticotropin without gross adjustments in dosage requirement.

Actions and Uses—See the monograph on corticotropin. Purified corticotropin has the advantage of causing fewer sensitization reactions than corticotropin. When administered in the form of a gel containing 150 mg. of gelatin per cubic centimeter, the total daily dosage of purified corticotropin may be given in one dose and adrenocorticotrophic activity persists for approximately 18 to 24 hours.

Dosage—As the dosage of purified corticotropin is expressed in clinical equivalents of U.S.P. units of corticotropin, it should be

employed in the same dosage as corticotropin when administered intramuscularly or subcutaneously. If administered by the intravenous route, three clinical equivalents of purified corticotropin must be administered to obtain the same range of clinical activity as obtained with each U.S.P. unit of corticotropin. As the gel, the entire daily dosage may be administered intramuscularly or subcutaneously at 24-hour intervals.

THE WILSON LABORATORIES

Purified Corticotropin-Gel: 5 cc. vials When administered intramuscularly or subcutaneously, each cubic centimeter is clinically equivalent to 20, 40, 80 or 100 U.S.P. units of corticotropin Preserved with 0.5 per cent phenol.

VASOPRESSIN TANNATE.—*Pitressin Tannate* (PARKE, DAVIS).— β -Hypophamine tannate.—Vasopressin tannate is the water-insoluble tannate of the pressor principle of the posterior lobe of the pituitary body of healthy domesticated animals used for food by man

Vasopressin tannate is assayed biologically

Actions and Uses.—Vasopressin tannate raises blood pressure, increases the muscular activity of the bladder and intestinal tract and exerts an antidiuretic effect in diabetes insipidus. (See the general statement on the pituitary gland.) The action of vasopressin tannate is more prolonged than that of vasopressin, and it is used, therefore, when prolonged action is desired, particularly for the treatment of patients suffering from diabetes insipidus

Dosage.—0.3 to 1 cc. (1.5 to 5 pressor units) of a solution is given by intramuscular injection at intervals of 36 to 48 hours *Never administer vasopressin tannate intravenously.*

PARKE, DAVIS & COMPANY

Suspension Pitressin Tannate in Oil: 1 cc. ampuls A suspension in peanut oil containing vasopressin tannate equivalent in activity to 5 pressor units of vasopressin in each cubic centimeter.

U. S. patent 2,399,742 U. S. trademark 254,507.

PLACENTA

Gonadotropic Substances

There are three types of biologic substances which stimulate the gonads of either sex. The fundamental physiologic gonadotropic hormone of the normal animal body is produced by the anterior pituitary. The chemical nature of this material is unknown, but it is established that there are two distinct components in the pituitary gonadotropic hormone.

The serum of the pre-
stance whose action is
from the anterior lobe.
to a point where very little inert protein accompanies the active
gonadotropic substance. It is probable that only one active com-

pound is involved. An international unit of this substance was defined by the special committee of the League of Nations, by comparison with a dry powder preparation supposed to be of stable potency.

The urine of pregnant women contains a gonadotropic substance distinct from that in the serum of the pregnant mare. The latter substance does not pass out into the mare's urine in appreciable amounts, whereas abundant amounts of the hormone called chorionic gonadotropic substance appear in the urine of pregnant women.

Injection of pregnancy urine, or certain extracts thereof, in rodents induces follicular growth and corpus luteum formation. When the gonadotropic activity of pregnancy urine first was demonstrated by Zondek, it was believed that the anterior pituitary secreted the substance responsible. On the basis of its effect in the rat, mouse and rabbit, the concept was advanced that this gonadotropin consisted of two hormones—prolan A, the follicle-stimulating hormone and prolan B, the luteinizing hormone. Further experimentation, however, has revealed that this substance is a single entity, that it arises from the placenta rather than from the pituitary and that it differs fundamentally from the gonadotropins of the anterior lobe. This substance is the basis of the Aschheim-Zondek test for pregnancy.

A significant physiologic difference between chorionic gonadotropin and preparations from the anterior pituitary is the inability of the former to stimulate appreciably the ovary of the hypophysectomized rat, the monkey or the human being. Injection of chorionic gonadotropin into primates will not induce follicular growth or corpus luteum formation. On the contrary, reliable investigators have observed definite degenerative changes in the ovaries of women and monkeys treated with this substance. Furthermore, no clear-cut endometrial responses have been observed in primates treated in this manner, which indicates conclusively the inability of this substance to stimulate the growth of normal ovarian structures. In the monkey and in the human being, chorionic gonadotropin will enhance and prolong the secretion of the corpus luteum. Probably the normal role of this hormone is to maintain the function of the corpus luteum during early pregnancy.

The physiologic action of chorionic gonadotropin is not limited to the female. It acts also on the interstitial cells of the testes, causing them to elaborate the androgenic hormone of the testis, which in turn induces growth of the accessory sex organs. This substance is effective in male monkeys and human beings. Among the reactions induced in the prepubertal monkey is the descent of the testes. In some animals there may be some increase in the size of the seminiferous tubules, but there is little if any effect on the germinal epithelium. Spermatogenesis is maintained by chorionic gonadotropin in recently hypophysectomized rats, but it is not restored after atrophy or induced in normal immature rats.

The therapeutic application of chorionic gonadotropin has covered a wide range. Many of the trials have been unsound or improperly conceived. Its use in the treatment of ovarian disturbance,

for example, has no scientific rationale at the present time, although when it was first introduced for the treatment of these dysfunctions the physiologic basis for therapy appeared excellent.

CHORIONIC GONADOTROPIN.—*Entromone (Exdo).*—*Follutein (Squina).*—The water-soluble gonadotropic substance obtained from the urine of pregnant women by selective precipitation and fractionation procedures. It is a glycoprotein containing about 12 per cent of galactose. This preparation is standardized in international units. One international unit equals 0.1 mg. of a standardized powder (see Council Report, *J.A.M.A.* 113:2,418 [Dec. 30] 1939).

Physical Properties.—Chorionic gonadotropin is a relatively pure preparation in which the active material is a glycoprotein soluble in water. It is relatively unstable in aqueous solution and is prepared either as a powder or in glycerin solution to be diluted with saline at time of use.

Actions and Uses.—Chorionic gonadotropin is recommended in the treatment of cryptorchism where there are no anatomic lesions causing obstruction of testicular descent. The diagnosis of an anatomic lesion often can be made where this therapy fails. Thus the surgical treatment of cryptorchism may be instituted at an early age when it is found that hormonotherapy cannot induce descent. Excessive therapy may result in pseudopuberty and possibly other harmful reactions.

The diagnosis of cryptorchism should not include those cases that have been termed *pseudocryptorchids*, in which the testes are maintained in the inguinal canal as the result of reflex muscular spasm. It will be found that the testes return to the normal scrotal position with gentle handling and warmth.

Chorionic gonadotropin therapy in other disorders, including hypogonadism in the adult, still is considered experimental because of the lack of convincing data. Its value in the treatment of uterine bleeding of functional nature also is as yet unproved, although numerous reports on this therapy have appeared in scientific publications. Considerable disagreement exists regarding the type of bleeding benefited. There is less enthusiasm for this therapy at present than there was several years ago.

Dosage.—

tional units

may be dan.

8 weeks in the absence of progressive descent. Therapy should be discontinued on the development of signs of precocious maturity.

B. F. ASCHER & COMPANY, INC.

Lyophilized Chorionic Gonadotropin: 10 cc. vials containing 5,000

I. U. per

when dilu

tified wate

a potency

COLE CHEMICAL COMPANY

Chorionic Gonadotropin: 5,000 I. U. in 10 cc. vials. A powdered

ENDO PRODUCTS, INC.

Powder Entromone: 5,000 I. U. and 10,000 I. U., in 10 cc vials
A powdered preparation of chorionic gonadotropin, which when diluted with 9 cc of the accompanying isotonic solution of sodium chloride preserved with 0.4 per cent phenol, provides solutions having a potency of 500 or 1,000 I. U. in each cubic centimeter

U. S. patent 1,910,298 U. S. trademark 354,550

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Follutain: 1,000, 5,000 and 10,000 I. U. vials containing a powdered preparation of chorionic gonadotropin which, when diluted with the accompanying 10 cc of sterile distilled water containing 0.5 per cent phenol, provides a solution having a potency of 100, 500 and 1,000 I. U. per cubic centimeter, respectively

THE UPJOHN COMPANY

Powder Chorionic Gonadotropin. 5,000 I. U. in 10 cc vials A powdered preparation of chorionic gonadotropin which when diluted with the accompanying 5 cc (ampul) of injectable water provides a solution having a potency of 1,000 I. U. of chorionic gonadotropin in each cubic centimeter Preserved with 0.5 per cent of chlorobutanol.

TESTES

Testosterone, a sex hormone, has been isolated from testis

the male, seminal vesicles, prostate and penis undergo severe atrophy; libido and sexual activity are diminished. Parenteral and oral administration of androgenic preparations will restore these structures and functions to normal, but beneficial effects in castrates or eunuchoids are present only as long as replacement therapy is continued. Testosterone also has been shown to maintain spermatogenesis in the hypophysectomized animal if treatment is begun immediately after the operation. It suppresses sperm formation in the intact adult but permanent suppression has not been found. In adequate doses, this androgen is effective in selected cases of menorrhagia, metrorrhagia and dysmenorrhea and for postpartum inhibition of breast engorgement and lactation.

Both experimental and clinical experience indicate that increase in muscle mass and body weight accompany administration of androgen and are associated with retention of nitrogen, inorganic phosphorus, sulfate, chloride, sodium and potassium. Potassium, calcium, and sulphur are retained in a ratio similar to that found in protein tissue. These anabolic effects of androgens may be of value in certain clinical conditions particularly when complicated by androgen deficiency as indicated by low urinary excretion levels of 17-ketosteroids and by sparsity of axillary and pubic hair. These conditions include senile, postmenopausal and idiopathic osteoporosis, panhypopituitarism and, when accompanied by signs of androgen deficiency, Addison's disease, Cushing's syndrome and ovarian agenesis with dwarfism.

The androgens also have been employed in the palliation of advanced inoperable breast cancer. They produce varying degrees of symptomatic improvement, with alleviation of pain and increase in weight and appetite occurring in a high percentage of patients. Objective improvement occurs to a much lesser degree, calcification of osteolytic lesions being demonstrable in 20 per cent or less of the patients treated, often accompanied by increased hemopoiesis. Metastatic soft tissue lesions of various sites also may respond, however, central nervous system lesions rarely respond. Both symptomatic and objective improvement are temporary and seldom exceed a period of a year. The mechanism of action of androgens in breast cancer has not been explained satisfactorily, but may be due in part to their anabolic activity.

A spontaneous cessation of hormone release by the testis with aging has been recognized as a rare entity termed male climacteric or menopause. Symptoms are similar to those of the female menopause. In the vast majority of instances, the vague manifestations of a psychoneurosis are incorrectly confused with those of organic testicular disorder. Criteria for laboratory confirmation of the diagnosis of male climacteric are equally confused. At present, such diagnosis probably is not justified without the demonstration of castration levels of urinary gonadotropin, as in the female. Testosterone provides effective replacement therapy only in the true disorder.

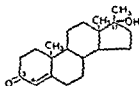
Relief of symptoms due to prostatism following treatment with testosterone has been claimed, but substantial evidence is lacking. Other claims made by promoters of this substance are unwarranted or concern uses that are still experimental.

Testosterone is not excreted in the urine, and should not be confused with the urinary androgens which have relatively little action

ciency of the testosterone is increased because its absorption from the site of injection is delayed by its combination with propionic acid. Methyltestosterone, a synthetic derivative, is much more active than testosterone when given orally, but their physiologic actions are similar. Androgens, like estrogens, preferably are ad-

ministered orally, unless this route is contraindicated. Testosterone is effective to a limited extent by percutaneous and sublingual administration. Pellet implantation also is used occasionally.

METHYLTTESTOSTERONE-U.S.P. — 17-Methyltestosterone — 17-Methyl- Δ^4 -androstene-17(α)-ol-3-one — The structural formula of methyltestosterone may be represented as follows:



Physical Properties — Methyltestosterone occurs as white or creamy-white crystals or crystalline powder. It is odorless and is stable in air, it is affected by light. It is insoluble in water, it is soluble in alcohol, methanol, ether and other organic solvents and sparingly soluble in vegetable oils.

Actions and Uses — Methyltestosterone may be given orally in the treatment of gonadal failure in the male. Its actions and uses are qualitatively the same as those of testosterone propionate. Methyltestosterone also is useful for the treatment of the female in the control of menorrhagia and metrorrhagia and in postpartum inhibition of lactation or breast engorgement. A unique and rare type of jaundice has been described, which occurs during therapy, and has obstructive and hepatic features.

Dosage — The dosage and duration of methyltestosterone therapy vary considerably, depending upon the condition, its severity, previous androgenic administration and individual variation. It is usually preferable to begin therapy with full doses of 30 to 50 mg. daily in divided dosage. For suppression of breast engorgement 25 to 30 mg. every 4 hours or three times daily for five or six doses should be administered starting at the beginning of lactation, i.e., the third or fourth day after delivery.

THE ECKON COMPANY, INC.

Tablets Methyltestosterone 10 mg.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Methyltestosterone 10 mg.

PRIMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Methyltestosterone: 10 and 25 mg.

S. J. TUTT & COMPANY

Tablets Methyltestosterone 10 mg.

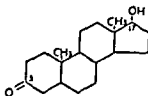
THE UPGON COMPANY

Tablets Methyltestosterone 10 and 25 mg.

WHITE LABORATORIES, INC.

Tablets Methyltestosterone: 10 and 25 mg.

STANOLONE.—*Noodrol* (Pfizer).—*Androstane-17(β)-ol-3-one*.
The structural formula of stanolone may be represented as follows:



Physical Properties.—Stanolone is a white, odorless, crystalline powder, with a melting point between 175 and 183°. It is practically insoluble in water. The approximate amounts that dissolve at 25° in the following solvents to form 100 cc. of solution are: 6 Gm. in alcohol and 1.5 Gm. in ether.

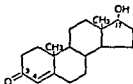
Actions and Uses.—Stanolone is an androgen that has the same actions and uses as testosterone and its esters. (See the general statement on testes.) It is useful clinically for its anabolic and tumor-suppressing actions in selected cases of inoperable carcinoma of the breast or postoperative metastatic carcinoma of the breast. Its use, which must be weighed against its inherent virilizing and metabolic effects, should be subject to the same precautions and contraindications as is the use of other androgenic agents.

Dosage.—Stanolone is administered by intramuscular injection. Like free testosterone, an aqueous suspension of microcrystalline stanolone should be expected to produce a slightly less intense and slightly more prolonged androgenic action than an equivalent oil solution of its propionic acid ester. In carcinoma of the breast, the average effective dosage is 100 mg. daily. This dosage should be continued as long as the patient shows improvement or until the patient is unable to tolerate androgenic therapy because of severe virilization or untoward metabolic effects. Lower dosage may be tolerated better but is considered ineffective against carcinoma of the breast. The dosage for the treatment of testicular or postpartum sup-
established by experi-

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

Suspension *Noodrol*: 10 cc. vials. A saline suspension containing 50 mg. of stanolone in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

TESTOSTERONE-U.S.P.—*Androlin* (Lincoln).—*Testrone* (Miltex).—The structural formula of testosterone may be represented as follows:



Physical Properties.—Testosterone occurs as white or slightly creamy white crystals or as a crystalline powder. It is odorless and is stable in air. Testosterone is insoluble in water. One gram dissolves in about 6 cc. of dehydrated alcohol, in 2 cc. of chloroform and in about 100 cc. of ether. It is soluble in dioxane and in vegetable oils.

Actions and Uses.—Testosterone is responsible for the actions of its derivative, testosterone propionate, and shares its uses. Testosterone in aqueous suspension apparently has a slightly lesser intensity and a slightly greater duration of androgenic action than testosterone propionate.

Dosage.—See the monograph on testosterone propionate.

BIO-INTRASOL LABORATORIES, INC.

Aqueous Suspension Testosterone with Procaine Hydrochloride 1%: 10 cc. vials. A suspension containing 25 or 50 mg. of testosterone in each cubic centimeter. Preserved with 0.01 per cent thimerosal.

LINCOLN LABORATORIES, INC.

Aqueous Suspension Androlin: 10 cc. vials. A suspension containing 25 or 50 mg. of testosterone in each cubic centimeter. Preserved with 0.01 per cent thimerosal.

METROPOLITAN LABORATORIES, INC.

Aqueous Suspension Testosterone with Benzyl Alcohol 2%: 10 cc. vials. A suspension containing 25, 50 or 100 mg. of testosterone in each cubic centimeter.

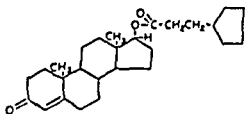
MEYER CHEMICAL COMPANY

Aqueous Suspension Testosterone: 10 cc. vials. A suspension containing 25 or 50 mg. of testosterone in each cubic centimeter. Preserved with 0.01 per cent thimerosal.

E. S. MILLER LABORATORIES, INC.

Aqueous Suspension Testrone: 10 cc. vials. A suspension in isotonic saline solution containing 25 or 100 mg. of testosterone in each cubic centimeter. Preserved with 0.01 per cent thimerosal.

TESTOSTERONE CYCLOPENTYLPROPIONATE.— Δ^1 -Androstene-17(β)-cyclopentylpropionate-3-one—The structural formula of testosterone cyclopentylpropionate may be represented as follows.



Physical Properties.—Testosterone cyclopentylpropionate is an off-white, odorless, tasteless, crystalline powder. It melts between 93 and 101°. It is freely soluble in alcohol, chloroform and ether, soluble in vegetable oils and slightly soluble in water.

Actions and Uses.—The actions and uses of testosterone cyclopentylpropionate are qualitatively the same as those of testosterone propionate, but it possesses the advantage of a more protracted androgenic effect. See the monograph on testosterone propionate.

Dosage.—Testosterone cyclopentylpropionate is administered intramuscularly in doses ranging from 10 to 50 mg. at intervals of 7 to 14 days. For induction of pubescence in eunuchoidism, 25 to 50 mg. once weekly may be required for several weeks. In eunuchism, 100 to 150 mg. may be employed at weekly intervals. For relief of constitutional symptoms resulting from deficiency of testicular function, 25 mg. every 2 weeks may be ample. Maintenance dosage must be determined by trial and error for each patient, utilizing the smallest dose and longest time interval between injections consonant with satisfactory control.

Because of the likelihood of virilism, it is advisable not to exceed a monthly dosage of 150 mg. in the treatment of gynecologic conditions. In the treatment of menorrhagia, 25 mg. administered approximately 1 week before the anticipated menses usually will control excessive bleeding. For metrorrhagia, 25 mg. should be administered at intervals of 1 to 2 weeks, but this dose may be increased to 50 mg. if necessary to control bleeding. In the treatment of atrophic vaginitis, 25 mg. administered at intervals of 1 to 2 weeks may be sufficient to control engorgement, discharge, and itching. In the treatment of dyspareunia, 25 mg. administered at intervals of 1 to 2 weeks may be sufficient to control dyspareunia. In the treatment of menopause, 25 mg. administered at intervals of 1 to 2 weeks may be sufficient to control the symptoms of menopause. Experience is lacking for recommendation of dosage for palliation of breast cancer.

THE UPJOHN COMPANY

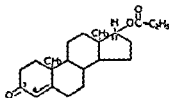
Solution Depo-Testosterone Cyclopentylpropionate in Oil: 10 cc vials. A solution in cotton-seed oil containing 50 or 100 mg. of testosterone cyclopentylpropionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

1 cc. vials: A solution in cotton-seed oil containing 0.1 Gm. of testosterone cyclopentylpropionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

U. S. trademark 515,760

TESTOSTERONE PROPIONATE—U. S. P.— Δ^4 -Androstene-17(α)-propionate-3-one—Testosterone propionate possesses androgenic properties. It may be prepared synthetically from cholesterol as

the starting material or from testosterone isolated from bull testes. The structural formula of testosterone propionate may be represented as follows.



Physical Properties.—Testosterone propionate occurs as white or slightly yellow crystals or crystalline powder. It is odorless and is stable in air. It is insoluble in water but freely soluble in alcohol, ether and other organic solvents. It also is soluble in vegetable oils.

Actions and Uses.—Testosterone propionate is primarily useful to supply testicular hormone for the treatment of deficiency or absence of this internal secretion of the male. Therefore, it may be of value in the treatment of prepuberal and postpuberal eunuchoidism or hypogonadism (deficiency states) and after castration or eunuchism due to other causes. In the latter instances treatment is replacement therapy, beneficial only as long as it is continued.

The use of testosterone propionate in eunuchoidism is intended to promote the development of primary and secondary sexual characteristics of patients with organic testicular failure, after the age of 16 or 17 when puberty has not occurred spontaneously and to relieve postpuberal constitutional symptoms attributable to deficient secretion. It is unwise to stimulate full sexual maturity in youths who are psychologically and otherwise physically unprepared for adult life.

The use of testosterone in cryptorchism is subject to certain qualifications, for example, hormonal therapy cannot be effective in this condition when there is an anatomic lesion causing obstruction of testicular descent. Testosterone propionate also is useful for the treatment of the female in the control of menorrhagia and metrorrhagia and in postpartum inhibition of lactation or breast engorgement.

For use in castrates and other effects, see general statement on testes.

Testosterone propionate may be tried in the palliation of advanced metastatic carcinoma of the female breast if the patient is considered beyond the help of either surgery or roentgen irradiation. Approximately one-half of the patients so treated experience partial or complete relief of symptoms for periods up to 1 year or more. Occasionally temporary regression of metastatic soft tissue or bone lesions may be observed.

Any patient under treatment with testosterone propionate must be watched carefully for signs of hypercalcemia, edema or acceleration of the disease. Hypercalcemia of severe proportions and acceleration of the disease are contraindications to continuation of

eruptions and itching or acne of the skin.

Dosage.—Testosterone propionate is administered intramuscularly in doses ranging from 10 to 50 mg. two to six times weekly, depending on the response obtained. To induce pubescence in eunuchoidism, 25 mg. three times weekly may be employed over a period of several weeks. To relieve gonadal insufficiency, as little as 10 mg. may be given three times weekly as a maintenance dose.

The dosage should be adjusted according to the condition and the effect desired. Priapism is indicative of excessive dosage and an indication for temporary withdrawal of the drug. There has been reported the induction of significant degrees of virilism in women when the amounts of an androgen administered were considerable (350 to 400 mg. testosterone propionate per month). For the treatment of menorrhagia, 25 mg. three times weekly before the onset of menstruation may be employed. For hypogonadism, 25 mg. on alternate days may be given. For impotence, 150 mg. is recommended. For suppression of lactation or breast engorgement, 50 to 75 mg. over a period of 2 or 3 days, starting on the third or fourth day after delivery.

The usual dosage employed for palliation of breast cancer is 150 to 300 mg. of testosterone propionate weekly given in three divided doses; the total duration of therapy is not fully established. At least 2 months of therapy appear to be necessary for a satisfactory subjective response and at least 5 months for any objective response.

THE BIO-INTRASOL LABORATORIES, INC.

Solution Testosterone Propionate in Oil with Benzyl Alcohol 4%: 10 cc. vials. A solution in sesame oil containing 50 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Solution Testosterone Propionate in Oil with Benzyl Alcohol 2%: 10 cc. vials. A solution in sesame oil containing 25 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Aqueous Suspension Testosterone Propionate with Procaine Hydrochloride 1%: 10 cc. vials. A suspension in isotonic saline solution containing 25 mg. of testosterone propionate in each cubic centimeter. Preserved with thimerosal 1:10,000.

THE BLUE LINE CHEMICAL COMPANY

Solution Testosterone Propionate in Oil with Benzyl Alcohol 3%: 10 cc. vials. A solution in corn oil containing 25 or 50 mg. of testosterone propionate in each cubic centimeter.

CARLO ERBA, INC.

Solution Testosterone Propionate in Oil with Benzyl Alcohol 2%:

10 cc. vials. A solution in peanut oil containing 25 or 50 mg. of testosterone propionate in each cubic centimeter Preserved with 0.5 per cent chlorobutanol.

GILBERT, ALLEN & COMPANY

Solution Testosterone Propionate in Oil: 10 cc. vials. A solution in sesame oil containing 25 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.1 per cent propylparaben.

Solution Testosterone Propionate in Oil with Benzyl Alcohol 4%: 10 cc. vials. A solution in sesame oil containing 50 mg. of testosterone propionate in each cubic centimeter.

GOLD LEAF PHARMACEUTICAL COMPANY

Solution Testosterone Propionate in Oil: 1 cc. ampuls and 10 cc. vials. A solution in sesame oil containing 10 mg. of testosterone propionate in each cubic centimeter.

1 cc. ampuls, and 10 and 30 cc. vials. A solution in sesame oil containing 25 mg. of testosterone propionate in each cubic centimeter.

10 and 30 cc. vials. A solution in sesame oil containing 50 mg. of testosterone propionate in each cubic centimeter.

C. F. KIRK COMPANY

Solution Testosterone Propionate in Oil: 10 cc. vials. A solution in sesame oil containing 25 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.1 per cent propylparaben.

METROPOLITAN LABORATORIES, INC.

Solution Testosterone Propionate in Oil. 10 cc. vials. A solution in sesame oil containing 25 or 50 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

PHYSICIANS' DRUG & SUPPLY COMPANY

Solution Testosterone Propionate in Oil: 10 cc. vials. A solution in peanut oil containing 25 or 50 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Solution Testosterone Propionate with 3% Benzyl Alcohol: 10 cc. vials. A solution in sesame oil containing 25 or 50 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.1 per cent propylparaben.

SMITH-DORRIS, DIVISION OF THE WANDER COMPANY

Solution Testosterone Propionate in Oil with Benzyl Alcohol 3%: 10 cc. vials. A solution in persic oil containing 25 mg. of testosterone propionate in each cubic centimeter.

TESTACAR & COMPANY, INC.

Solution Testosterone Propionate in Oil: 10 and 30 cc. vials.

A solution in peanut oil containing 25 mg. of testosterone propionate in each cubic centimeter.

10 cc. vials. A solution in peanut oil containing 50 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Solution Testosterone Propionate in Oil with Benzyl Alcohol 10%: 1 cc. ampuls and 10 cc. vials. A solution in sesame oil containing 0.1 Gm. of testosterone propionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

S. J. TUTAG & COMPANY

Solution Testosterone Propionate in Oil with Benzyl Alcohol 3%: 10 cc. vials. A solution in sesame oil containing 25 or 50 mg. of testosterone propionate in each cubic centimeter.

THE UPJOHN COMPANY

Solution Testosterone Propionate in Oil: 1 and 10 cc. vials. A solution in cottonseed oil containing 25 mg. of testosterone propionate in each cubic centimeter

10 cc. vials. A solution in cottonseed oil containing 50 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

THE VITARINE COMPANY

Solution Testosterone Propionate in Oil: 1 cc. ampuls and 10 cc. vials. A solution in sesame oil containing 10 or 25 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.1 per cent propylparaben.

Solution Testosterone Propionate in Oil with Benzyl Alcohol 4%: 1 cc. ampuls and 10 cc. vials. A solution in sesame oil containing 50 mg. of testosterone propionate in each cubic centimeter.

WHITE LABORATORIES, INC.

Solution Testosterone Propionate in Oil: 1 cc. ampuls. A solution in sesame oil containing 25 mg. of testosterone propionate in each cubic centimeter.

10 cc. vials. A solution in sesame oil containing 10 mg. of testosterone propionate in each cubic centimeter. Preserved with phenyl mercuric borate 1:50,000.

10 cc. vials. A solution in sesame oil containing 25 mg. of testosterone propionate in each cubic centimeter.

Solution Testosterone Propionate in Oil with Benzyl Alcohol 3%: 6 and 10 cc. vials. A solution in sesame oil containing 50 mg. of testosterone propionate in each cubic centimeter. Preserved with phenyl mercuric borate 1:50,000

THYROID

Thyroid acts through the thyroxin contained in it. It increases metabolism, as indicated by loss of body weight and increase of

urinary nitrogen, carbon dioxide production, and oxygen assimila-

ousness, tremors, headache, flushing of the surface, sweating and much more pronounced loss of weight.

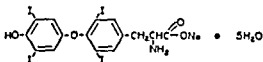
Thyroid is used in deficient action of the gland. The most striking results are obtained in cretinism and myxedema and in the condition known as cachexia thyreopriva, due to the removal of the thyroid gland. The beneficial effects are seen in the improved condition of the skin, the re-establishment of perspiration and of

normal state; it is often necessary, however, to continue such small doses indefinitely.

In some forms of goiter the function of the thyroid is defective,

so as not to do harm by the destruction of proteins. The effects, which may be pronounced at first, are not permanent.

SODIUM LEVOTHYROXINE—Synthroid Sodium (TRAVENOL)—3,3',5,5'-tetraiodothyronine pentahydrate—The structural formula of sodium levothyroxine may be represented as follows:



Physical Properties—Sodium levothyroxine is a light yellow to buff, odorless, tasteless powder. It is very slightly soluble in chloroform and in ether. The approximate amounts that dissolve at 25° in 10 cc of the following solvents are: 0.4 Gm in alcohol and 0.2 Gm in water. Sodium levothyroxine is hygroscopic, but it is stable in dry air and at room temperature. The pH of a saturated solution is between 8.35 and 9.35.

Actions and Uses—Sodium levothyroxine is the sodium salt of the levo isomer of thyroxine (DL-thyroxine). Levothyroxine exhibits approximately twice the activity of the racemic (DL-) form. Sodium levothyroxine, which is more soluble and reportedly more active than the base, levothyroxine, also is more efficiently absorbed by the gastro intestinal tract and is effective in smaller oral doses than mixtures of D-thyroxine and L-thyroxine (thyroxine-U.S.P. XIII, thyroxin fraction-N.N.R. 1947). Approximately 50

Micro-organisms vary in their antigenic (antibody stimulating) property and, therefore, vaccines prepared from some strains and species are not efficient immunizing agents. There also are differences between human beings, and animals, in their response (i.e., antibody production) to a given vaccine. In acute conditions, it is often undesirable to depend upon this method of active immunization since antibody formation may be too slow to affect the disease. These limitations render passive immunization for bacterial serums, antitoxins and other products an available method for the prophylaxis of infectious diseases.

Federal regulations control the manufacture and sale of these potent, and in some cases, dangerous products; firms are licensed, under the supervision of the National Institutes of Health of the United States Public Health Service, to import, export or sell these biologic products in interstate commerce. Information regarding tests and standards required by law may be obtained from that agency. The Council considers only licensed biologic products for inclusion in *New and Nonofficial Remedies*.

A number of these products may cause untoward reactions when they are administered as therapeutic or prophylactic agents. Individual sensitivities to animal products, especially horse serum and egg, are primarily responsible for adverse symptoms, and idiosyncrasies toward the products of bacterial metabolism are responsible for others. The Council requires that the labeling and directive literature for all products indicate possible dangerous side reactions.

Although normal human whole blood, serum and plasma may contain antibodies with immunologic properties comparable to those of the above preparations, the low concentrations and instability of the antibodies in those products preclude their utilization for immunization against infectious diseases. Normal blood fractions are described in the chapter on blood derivatives and plasma substitutes.

IMMUNE SERUMS

Intentional passive immunization against infectious diseases can be effected by parenteral administration of blood serum and its fractions obtained from immune human beings or animals which survived specific natural or artificial infection. The immune substances, antibodies, contained in those fractions either neutralize the metabolic products (toxins) of the micro-organisms or inhibit the growth of the infectious agent.

Toxins are metabolic products excreted by or inherent in some micro-organisms, plants and animals. Examples are the soluble exotoxins excreted by the diphtheria and tetanus bacilli. Antitoxins are prepared for human therapy by immunizing animals against specific toxins.

Immune serums and serum fractions that inhibit the metabolism of pathogenic micro-organisms in the animal body are obtained from human beings and animals following natural or

artificial infection with bacteria and viruses. The antibody titer in immune blood donors may be increased by injection of the specific killed or attenuated micro-organisms. Such serums contain antibodies for all components of the micro-organism (i.e., cell wall, flagella, endotoxins, etc.).

Horses and rabbits are the animals utilized for the artificial production of immune serums. One inoculation with the animal products may sensitize a patient to the blood components of that species, and subsequent inoculations of products from the same animal source may cause serum sickness or anaphylactoid shock. Temporary desensitization can be induced by repeated injections of minute doses or by the use of alternate routes of administration (i.e., subcutaneous) which ensure slow absorption; prevention of the rapid accumulation of antigen in the circulating blood is essential.

The gamma globulin fraction of human blood has been found to contain specific antibodies in the greatest concentration. (See the chapter on blood derivatives and plasma substitutes.)

Because ultraviolet irradiation currently employed for the sterilization of human blood products has not proved as efficient as indicated by previous studies, minimum requirements pertaining to all pooled human serums require a warning statement to the effect that the product may contain the virus of homologous serum hepatitis.

Animal Source

ANTISERUM FOR THE TREATMENT OF INFLUENZA MENINGITIS DUE TO *H. INFLUENZAE* TYPE B

Actions and uses.—Anti-hemophilus influenzae type B serum is used for treatment of influenzal meningitis due to *H. influenzae* type B organisms.

Dosage.—After identification of the causative *H. influenzae*, type B, the dosage of serum is determined by estimating the level of spinal fluid dextrose in milligrams per 100 cc. since this varies inversely with the severity of the infection.

SPINAL FLUID DEXTROSE	DOSAGE OF SERUM
Under 15 mg. per 100 cc.	100,000 units
15 to 25 mg. per 100 cc.	75,000 units
25 to 40 mg. per 100 cc.	50,000 units
Over 40 mg. per 100 cc.	25,000 units

The dose is diluted in isotonic sodium chloride solution or Ringer's solution, 10 cc. of solution per kilogram of body weight, and administered intravenously with the speed adjusted so that administration is completed within 2 hours. Adjunctive treatment with chlorotetracycline hydrochloride, streptomycin salts or sulfadiazine sodium is recommended.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Anti-Hemophilus Influenzae Type B Serum (Rabbit): 25 cc. vials. Each vial contains 25 mg. agglutinin antibody nitrogen equivalent to not less than 25,000 provisional units. Preserved with thimerosal 1:10,000 and 0.2 per cent of phenol.

ANTIVENIN (LATRODECTUS MACTANS).—An antitoxic serum prepared by immunizing horses against the venom of the black widow spider (*Latrodectus mactans*).

Actions and Uses.—Standardized on the basis of its ability to neutralize the venom of the black widow spider when the two are injected simultaneously in mice, this material is indicated in the treatment of symptoms due to bites inflicted by the black widow spider (*Latrodectus mactans*). Prior to use, tests for serum sensitivity should be made, test material consisting of 1:10 dilution of isotonic solution of normal equine serum, which is injected intradermally. The amount of material injected into the skin for the intradermal test should be not more than 0.02 cc. of the test material. The result can be evaluated in 10 minutes, a positive reaction consisting of an urticarial wheal surrounded by a zone of erythema.

If there is a negative result from the skin test, the therapeutic serum can be administered. If there is a positive skin reaction, an

... of the test material on the

istering the serum.

Associated treatment includes hot plunge baths and intravenous injection of 10 per cent calcium gluconate. Barbiturates may be used to treat restlessness. Apparently nothing is gained by local treatment at the site of the bite.

Dosage.—An injection of 2.5 cc. of serum is administered intramuscularly.

SHARP & DOHME, DIVISION OF MERCK & Co, INC.

Lyovac Antivenin (*Latrodectus mactans*): Vacule vial containing a sufficient amount of lyophilized antivenin to yield 25 cc. of restored double-concentrated antivenin with 0.01 per cent thimerosal as a preservative; packaged with a 2.5 cc. vial of distilled water and one 1 cc. vial of normal horse serum (diluted 1:10) as test and desensitizing material.

Human Source

HUMAN MEASLES IMMUNE SERUM.—Measles Convalescent Serum.—Human measles immune serum is sterile serum obtained from the blood of a healthy human who has survived an attack of measles.

Physical Properties.—Human measles immune serum is a transparent or slightly opalescent liquid of a faint brownish, yellowish

or greenish color, nearly odorless or having an odor due to the presence of a preservative. It may have a slight, granular deposit. Human measles immune serum must be free from harmful substances detectable by animal inoculation and must not contain an excessive proportion of preservative (not more than 0.5 per cent of phenol or 0.4 per cent of cresol, if either of these is used).

Human measles immune serum also may be produced as a dry, white or slightly gray powder. The addition of distilled water or other suitable solvent to the dry preparation will produce a liquid which has the characteristics and meets all the requirements

of 6 years or under, 10 cc. is given intramuscularly within 5 days after exposure. For children between 7 and 12 years of age, 15 cc. is given and for older children and adults, 20 cc.

The serum may be given intravenously or intramuscularly. Vacuum dried serum should be given only intramuscularly.

Whether the serum is given for prevention or modification depends on the number of days the patient has been exposed. If prevention is desired, however, the dosage may have to be increased to correspond with the length of time that has elapsed since exposure of the patient. If injection is made on the sixth or seventh day after exposure, a high percentage of patients have a modified type of measles which is followed by lasting immunity. It is probable that serum given after the seventh day following the initial exposure has little effect in either preventing or modifying the disease.

Dosage.—Usual, parenteral, therapeutic, 20 cc.; prophylactic, 10 cc.

MILWAUKEE BLOOD CENTER, INC.

Measles Immune Serum (*Human*): 5 and 10 cc. vials.

MICHAEL REESE RESEARCH FOUNDATION

Human Measles Immune Serum: 5, 7.5 and 20 cc. vials

PERTUSSIS IMMUNE HUMAN SERUM-U.S.P.—Pertussis Immune Serum (*Human*).—"Pertussis Immune Human Serum is the liquid or dried serum of blood obtained from donors who have recovered from pertussis and who for the preceding 7 or more days have been without fever or other active clinical manifestation of the disease, or from donors who have been actively immunized with pertussis vaccine. Pertussis Immune Human Serum is suitably irradiated with ultraviolet light and contains a suitable antibacterial agent approved by the National Institutes of Health." U.S.P.

Physical Properties.—Liquid pertussis immune human serum is a transparent or slightly opalescent liquid, having a yellow or deep pink color. It is nearly odorless or has an odor due to the preservative. The dried serum has a yellow, creamy or pink color.

Action and Use.—The unmodified serum, whether liquid or

dried, may be administered intravenously or intramuscularly for prophylaxis and treatment of "whooping cough." The refined and concentrated product may not be administered intravenously but is intended for both prophylactic and therapeutic use.

Dosage.—For treatment, three 20 cc. doses may be injected at 48-hour intervals. A fourth dose may be necessary. Critically ill infants may be given intravenous injections of 60 to 100 cc., the dose may be repeated one or more times.

The foregoing dosage applies only to the unmodified serum. The refined and concentrated serum is several times more potent than the unmodified product. The dosage recommended on the package label should be followed.

CUTTER LABORATORIES

Antipertussis Serum (*Hypertussis*) (Human): A highly purified and concentrated globulin prepared from human donors immunized with *H. pertussis* vaccine. Preserved with thimerosal 1:10,000. Each vial contains 2.5 cc., which represents the initial dose. Dose may be repeated as often as indicated by the condition of the patient.

MILWAUKEE BLOOD CENTER, INC.

Pertussis Immune Serum (Human): 10 and 20 cc. vials.

PHILADELPHIA SERUM EXCHANGE, THE CHILDREN'S HOSPITAL OF PHILADELPHIA

Pertussis Immune Serum (Human): 20 cc. Desi-Pak Vials containing dried ultraviolet irradiated serum.

HUMAN SCARLET FEVER IMMUNE SERUM.—Scarlet Fever Convalescent Serum.—Human scarlet fever immune serum is a sterile serum obtained from the blood of a healthy human who has survived an attack of scarlet fever.

Physical Properties.—Human scarlet fever immune serum is a transparent or slightly opalescent liquid of a faint brownish, yellowish or greenish color, nearly odorless or having an odor due to the presence of a preservative; it may have a slight, granular deposit.

Actions and Uses.—Human scarlet fever immune serum is of value in transferring passive immunity to a patient exposed to scarlet fever. The evidence as to therapeutic activity is conflicting. It may be used in patients sensitive to horse serum, though the antitoxic content of convalescent serum is low. It is not adequate to meet septic complications.

Dosage.—Usual, parenteral, therapeutic, 20 cc.; prophylactic, 10 cc.

MILWAUKEE BLOOD CENTER, INC.

Scarlet Fever Immune Serum (Human): 10 and 20 cc. vials.

MICHAEL REESE RESEARCH FOUNDATION

Human Scarlet Fever Immune Serum: 10 and 20 cc. vials.

IMMUNE SERUM GLOBULIN-U.S.P.—Immune Serum Globulin

(Human) —Measles Prophylactic —“Immune Serum Globulin is a sterile solution of globulins which contains those antibodies normally present in adult human blood. It contains a suitable antibacterial agent. Each lot of Immune Serum Globulin is derived from an original plasma or serum pool which represents at least 1,000 individuals. Not less than 90 per cent of the total protein of Immune Serum Globulin is globulin.” *U.S.P.*

Physical Properties —Immune serum globulin (human) is a transparent or slightly opalescent liquid, either colorless or of a brownish color due to denatured hemoglobin. It is nearly odorless and may develop a slight granular deposit on aging.

necessarily modified in accordance with the stage of the incubation period or the prodromal stage of the disease. In the prevention of measles in institutional cases larger doses are required than those given for modification. Prevention is, of course, less desirable than modification except where younger children ill with other diseases are apt to contract measles by exposure to a modified case. Otherwise it is more desirable to permit a child to have mild measles so that immunization occurs than to prevent the disease and leave the child nonimmune to subsequent attacks of the disease. Protection should not be attempted until definite exposure has taken place. Attempts to avoid reactions have led to refinement and concentration of the product and even to its oral administration; the latter cannot be advocated on the basis of present evidence.

Dosage.—The amount of immune serum globulin (human) that should be injected depends on the following factors:

1. Whether modification or prevention is desired.
2. The age and general condition of the patient.
3. The intimacy of exposure.

Careful consideration of the available literature is necessary to evaluate these factors and determine an entirely satisfactory dosage, and even then it is not always possible to avoid prevention when modification is desired and vice versa. The following doses are recommended as a general pattern subject to adjustment in accordance with the factors listed above. For prevention, 2 to 10 cc., for modification, 2 to 5 cc.

CUTLER LABORATORIES

Immune Serum Globulin (*Human*): 2 and 10 cc. vials Preserved with thimerosal 1:10,000

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

Immune Serum Globulin (*Human*): 2 cc vials Preserved with thimerosal 1:10,000

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

Immune Serum Globulin (Human): 2 and 10 cc. vials. Preserved with thimerosal 1:10,000.

SHARP & DOHME, DIVISION OF MERCK & Co, INC.

Immune Serum Globulin (Human): 2 and 10 cc. vials. Preserved with thimerosal 1:10,000

Licensed by Research Corporation. U. S. patent 2,390,074.

POLIOMYELITIS IMMUNE GLOBULIN (HUMAN).—Poliomyelitis immune globulin (human) is a preparation of plasma or serum that contains antibodies against poliovirus. Each lot is derived from an original plasma or serum pool which represents at least 100 persons and contains 165 mg. (± 15 mg.) of antibody. It is also obtained from placenta. The content of poliovirus antibody is determined by the National Institutes of Health of the United States Public Health Service, including the release of each lot individually before its distribution.

Actions and Uses.—Poliomyelitis immune globulin (human) is a passive immunologic agent that contains significant concentrations of antibodies useful for the prevention of poliomyelitis, measles and infectious hepatitis, but temporary protection against poliomyelitis has been produced in man within a week following injection, but not against paralytic poliomyelitis.

It is less than the likelihood of securing protection against measles or infectious (epidemic) hepatitis by the same means. The preparation is equivalent in usefulness to immune serum globulin (human) for the prevention or modification of measles when injected within the first 6 days, but not beyond the tenth day, following initial exposure. It also prevents or attenuates infectious (epidemic) hepatitis when injected during the incubation period; apparently it confers passive immunity to that infection for 6 to 8 weeks.

Poliomyelitis immune globulin (human) is regarded as being free from the virus of serum hepatitis. Sensitization to repeated injections is extremely rare. Injections occasionally may be followed by local tenderness and stiffness of muscles persisting for several hours. Care should be exercised to avoid accidental intravenous administration.

Dosage.—Poliomyelitis immune globulin (human) is administered only by intramuscular injection, preferably in the buttock. *Careful technic is essential to avoid accidental intravenous injection.*

For protection against paralytic poliomyelitis, the average dose to be injected is calculated on the basis of 0.31 cc. per kilogram (0.14 cc. per pound) of body weight. This dose may be repeated in 6 weeks if continued protection is desirable.

For the modification of measles, the dose is calculated on the basis of 0.044 to 0.055 cc. per kilogram (0.02 to 0.0246 cc. per pound) of body weight; for complete prevention, at least 0.22 cc.

per 2 1/2-- dose
titis,
per pound)
adults, this dose should be repeated
in 3 weeks if longer protection is desired

CUTTER LABORATORIES

Poliomyelitis Immune Globulin (Human): 2 and 10 cc. vials. A solution containing about 165 mg of the globulin in each cubic centimeter. Preserved with 0.01 per cent thimerosal

TOXOIDS

A toxoid is a toxin modified to reduce its toxicity. Bacterial filtrates, containing toxins and other components of a liquid bacterial culture, can be rendered nontoxic, as measured by appropriate animal tests, without appreciable loss of their antigenic or combining values. Formaldehyde is the agent generally used for the detoxification of toxins.

Toxoids are supplied plain (synonyms crude, clear, fluid) and as precipitated and adsorbed preparations. Alum, $\text{AlK}(\text{SO}_4)_2 \cdot 12 \text{H}_2\text{O}$, is the chemical agent used for the precipitated products; aluminum hydroxide and aluminum phosphate are employed to provide an adsorption surface for toxoids. The precipitated and adsorbed products are absorbed more slowly by the circulating and tissue fluids of the body, and excreted slowly; therefore, they provide higher immunizing titers than does a plain toxoid. Nodules sometimes are observed after the injection of these more slowly absorbed products. Rarely, temporary liquefactions occur which should not be incised but allowed to disappear spontaneously. These phenomena are more frequent and appear earlier in the more superficial injections.

Combinations of toxoids from different bacterial species, as well as combinations of toxoids with bacterial vaccines, minimize the number of inoculations necessary to produce immunization against several infectious agents. It is claimed that such combinations provide more adequate specific immunization with higher antibody titer than the individual components given singly.

Single Toxoids

DIPHTHERIA TOXOID, ALUMINUM HYDROXIDE ADSORBED. USP.—"Aluminum Hydroxide Adsorbed Diphtheria Toxoid is a sterile suspension of diphtheria toxoid adsorbed on aluminum hydroxide from formaldehyde-treated solution of the products of growth of the diphtheria bacillus (*Corynebacterium diphtheriae*). It contains a non-pheno... 0.55 mg of aluminum in... substitute one injection" U. S.

Physical Properties.—Aluminum hydroxide adsorbed diphtheria toxoid is a turbid, white, slightly gray or slightly pink suspension.

Actions and Uses.—Aluminum hydroxide adsorbed diphtheria toxoid is used for active immunization against diphtheria. Since some local and general reactions have been observed in adults and in children over 8 years of age, an intracutaneous test dose of 0.1 cc of the toxoid diluted (1:20) with physiologic saline solution should be given to determine sensitivity in these persons. Because of the physical character of the aluminum hydroxide adsorbed product, absorption is delayed.

Dosage.—Usual, hypodermic, two injections of 0.5 or 1 cc, as specified in the labeling, 4 to 6 weeks apart.

CUTTER LABORATORIES

Diphtheria Toxoid, Alhydrox: 1 cc. vials (one immunization: two 0.5 cc. injections) and 5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000

DIPHTHERIA TOXOID, ALUMINUM PHOSPHATE ADSORBED.—Aluminum phosphate adsorbed diphtheria toxoid is a sterile suspension of diphtheria toxoid adsorbed on aluminum phosphate. It is detoxified and standardized for potency as described in the monograph on diphtheria toxoid, aluminum hydroxide adsorbed. Diphtheria toxoid, aluminum phosphate adsorbed, complies with the official potency and other requirements of the National Institutes of Health of the United States Public Health Service.

Actions and Uses.—See the monograph on diphtheria toxoid, aluminum hydroxide adsorbed. Because of the physical character of the adsorbed product, absorption is delayed.

Dosage.—Usual, hypodermic, two injections of 0.5 or 1 cc, as specified in the labeling, 4 to 6 weeks apart.

PARKE, DAVIS & COMPANY

Diphtheria Toxoid (Aluminum Phosphate Adsorbed): 1 cc. vial (one immunization, two 0.5 cc injections), and 5 cc vials (five immunizations) Preserved with thimerosal 1:10,000

TETANUS TOXOID-U.S.P.—"Tetanus Toxoid is a sterile solution of the formaldehyde-treated products of growth of the tetanus bacillus (*Clostridium tetani*). It contains not more than 0.02 per cent of residual free formaldehyde" U.S.P.

Physical Properties.—Tetanus toxoid is a brownish-yellow, clear or slightly turbid liquid having a characteristic odor or an odor due to the presence of a preservative. It must not contain an excessive proportion of preservative (not more than 0.5 per cent of phenol or 0.4 per cent of cresol if either of these is used) and must be free from harmful substances detectable by animal inoculation.

Actions and Uses.—Tetanus toxoid is used for active immunization against tetanus infection. Active immunization is a desirable procedure in the case of individuals who are subject to a greater than normal hazard of infection.

Dosage.—Usual, hypodermic, three injections of 0.5 or 1 cc, as specified in the labeling, 3 to 4 weeks apart.

CUTTER LABORATORIES

Tetanus Toxoid: 15 cc vials (one immunization) three 0.5 cc injections) and 15 cc vials (ten immunizations). Preserved with thimerosal 1:10,000

ELI LILLY & COMPANY

Tetanus Toxoid: 15 cc (one immunization) and 7.5 cc vials (five immunizations) Preserved with thimerosal 1:10,000.

U. S. STANDARD PRODUCTS COMPANY

Aquagen Tetanus Toxoid: 15 cc (one three-dose immunization), 7.5 cc (five three-dose immunizations) and 22.5 cc (fifteen three-dose immunizations) vials Preserved with thimerosal 1:10,000.

TETANUS TOXOID, ALUM PRECIPITATED-U.S.P.—"Alum Precipitated Tetanus Toxoid is a sterile suspension of tetanus toxoid precipitated by alum from a formaldehyde-treated solution of the products of growth of the tetanus bacillus (*Clostridium tetani*). It contains a suitable non-phenolic antibacterial agent approved by the National Institutes of Health, and not more than 15 mg of alum in the volume stated in the labeling to constitute one injection" U.S.P.

Physical Properties—Alum precipitated tetanus toxoid is a turbid, white, slightly gray or slightly pink suspension

Actions and Uses—See the monograph on tetanus toxoid. Because of the physical character of the alum precipitated product, absorption is delayed

Dosage—Usual, hypodermic, two injections of 0.5 or 1 cc, as specified in the labeling, 4 to 6 weeks apart

ELI LILLY & COMPANY

Tetanus Toxoid (Alum Precipitated) 1 cc (one immunization) and 5 cc vials (five immunizations) Preserved with thimerosal 1:10,000

NATIONAL DRUG COMPANY

Tetanus Toxoid (Alum Precipitated) Two 0.5 cc vials (one immunization) one 5 cc vial (five immunizations) and one 0.5 cc vial for supplementary dose Preserved with thimerosal 1:10,000.

PITTMAN MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC

Tetanus Toxoid (Alum Precipitated) 5 cc vials (five immunizations) Preserved with thimerosal 1:10,000

SQUIBB & DOWNS, DIVISION OF MERCK & CO., INC

Tetanus Toxoid (Purified Alum Precipitated) 1 cc vials (one two dose immunization) and 5 cc vials (five two dose immunizations) Preserved with thimerosal 1:10,000

F. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Tetanus Toxoid (Alum Precipitated) 10 cc vials for five immunizations (ten immunizing doses) Preserved with thimerosal 1:10,000

U. S. STANDARD PRODUCTS COMPANY

Aquagen Tetanus Toxoid (Alum Precipitated): 1 cc. (one two-dose immunization) and 5 cc. (five two-dose immunizations) vials. Preserved with thimerosal 1:10,000.

WYETH LABORATORIES, INC.

Tetanus Toxoid (Alum Precipitated Refined): 5 and 10 cc. vials. Preserved with 0.01 per cent thimerosal.

TETANUS TOXOID, ALUMINUM HYDROXIDE ADSORBED-U.S.P.

—"Aluminum Hydroxide Adsorbed Tetanus Toxoid is a sterile suspension of tetanus toxoid adsorbed on aluminum hydroxide from a formaldehyde-treated solution of the products of growth of the tetanus bacillus (*Clostridium tetani*). It contains a suitable non-phenolic antibacterial agent approved by the National Institutes of Health, and not more than 0.85 mg of aluminum in the volume stated in the labeling to constitute one injection." U.S.P.

Physical Properties.—Aluminum hydroxide adsorbed tetanus toxoid is a turbid, white, slightly gray or slightly pink suspension.

Actions and Uses.—See the monograph on tetanus toxoid. Because of the physical character of the aluminum hydroxide adsorbed product, absorption is delayed.

Dosage.—Usual, hypodermic, two injections of 0.5 or 1 cc., as specified in the labeling, 4 to 6 weeks apart.

CUTTER LABORATORIES

Tetanus Toxoid, Alhydrox: 1 cc. vials (one immunization: two 0.5 cc. injections) and 5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

Combinations of Toxoids

DIPHTHERIA AND TETANUS TOXOIDS-N.F.—"Diphtheria and Tetanus Toxoids is a clear or slightly turbid, yellowish or brownish suspension of diphtheria and tetanus toxoids adsorbed on aluminum hydroxide. It contains a suitable non-phenolic antibacterial agent approved by the National Institutes of Health, and not more than 0.85 mg of aluminum in the volume stated in the labeling to constitute one injection." U.S.P.

Actions and Uses.—Diphtheria and tetanus toxoids is used for the primary immunization of infants, children, and adults.

Intervals of 3 to 4 weeks between injections. Additional doses may be required to secure a negative Shick test.

ELI LILLY & COMPANY

Combined Diphtheria-Tetanus Toxoids: 1.5 cc. vials (one im-

munization) and 7.5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

PARKE, DAVIS & COMPANY

Combined Diphtheria-Tetanus Toxoids: 3.5 cc. vials (one immunization) and 7.5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

DIPHTHERIA AND TETANUS TOXOIDS, ALUM PRECIPITATED—U.S.P.—"Alum Precipitated Diphtheria and Tetanus Toxoids is a sterile suspension prepared by mixing suitable quantities of alum precipitated diphtheria toxoid and alum precipitated tetanus toxoid. The potency and the proportions of the toxoids are such as to provide an immunizing dose of each toxoid in the total dosage specified on the label Alum Precipitated Diphtheria and Tetanus Toxoids, U.S.P. Each vial contains enough for one injection" U.S.P.

Physical Properties—Alum precipitated diphtheria and tetanus toxoids is a turbid, white, slightly gray or slightly pink suspension.

Actions and Uses—See the monograph on diphtheria and tetanus toxoids. Because of the physical character of the alum precipitated product, absorption is delayed.

Dosage—Usual, hypodermic, two injections of 0.5 or 1 cc., as specified in the labeling, 4 to 6 weeks apart.

ELI LILLY & COMPANY

Combined Diphtheria-Tetanus Toxoids (*Alum Precipitated*): 1 cc. vials (one immunization) and 5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

NATIONAL DRUG COMPANY

Combined Diphtheria and Tetanus Toxoids (*Alum Precipitated*): Two 0.5 cc. vials (one immunization) and two 2.5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

PITMAN-MOORE COMPANY

Combined Diphtheria-Tetanus Toxoid (*Alum Precipitated*): 5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

E. R. SQUIBS & SONS, DIVISION OF OLEN MATHIESON CHEMICAL CORPORATION

Combined Diphtheria Toxoid-Tetanus Toxoid (*Alum Precipitated*): 5 cc (0.5 cc dose form) and 10 cc (1 cc dose form) vials five immunizations each. Preserved with thimerosal 1:10,000.

WYETH LABORATORIES, INC.

Combined Diphtheria-Tetanus Toxoid (*Alum Precipitated*): 1 and 10 cc vials in packages of two 1 cc vials and of one 10 cc vial. Preserved with 0.01 per cent thimerosal.

DIPHTHERIA AND TETANUS TOXOIDS, ALUMINUM HYDROXIDE ADSORBED-U.S.P.—"Aluminum Hydroxide Adsorbed Diphtheria and Tetanus Toxoids is a sterile suspension prepared by mixing suitable quantities of the aluminum hydroxide adsorbed forms of diphtheria and tetanus toxoids. The potency and the proportions of the toxoids are such as to provide one immunizing dose of each toxoid in the total dosage prescribed on the label. Aluminum Hydroxide Adsorbed Diphtheria and Tetanus Toxoids contains a suitable non-phenolic antibacterial agent approved by the National Institutes of Health, and not more than 0.85 mg. of aluminum in the volume stated in the labeling to constitute one injection" U.S.P.

Physical Properties.—Aluminum hydroxide adsorbed diphtheria and tetanus toxoids is a turbid, white, slightly gray or slightly pink suspension.

Actions and Uses.—See the monograph on diphtheria and tetanus toxoids. Because of the physical character of the aluminum hydroxide adsorbed product, absorption is delayed.

Dosage.—Usual, hypodermic, two injections of 0.5 or 1 cc., as specified in the labeling, 4 to 6 weeks apart.

CUTLER LABORATORIES

Diphtheria and Tetanus Toxoids Alhydrox: 1 cc vials (one immunization two 0.5 cc injections) and 5 cc vials (five immunizations). Preserved with thimerosal 1:10,000.

VACCINES

Vaccines are suspensions of either attenuated or killed microorganisms that are administered hypodermically for the prevention or treatment of infectious diseases. The use of vaccines provides a method for active immunization. See the general statement on immunologic agents.

Bacterial vaccines also are utilized for their pyrogenic (fever-producing) properties in certain noninfectious diseases.

Vaccines are prepared from bacterial, viral and rickettsial strains of micro-organisms.

Viral and rickettsial vaccines contain, in addition to the microorganisms, the components of artificially infected tissues (e.g., animal brain tissue and eggs) which are required for the production of those products; inoculation with such foreign proteins may produce dangerous side actions.

Bacterial vaccines are suspensions of micro-organisms which usually have been washed free of the components of the culture medium to reduce the danger of reactions to the antigens it may contain. Newer methods of bacterial vaccine processing provide for the incorporation of the "whole culture" (bacteria, metabolic products and culture medium) in the final product; synthetic culture media, containing hydrolyzed proteins which are less antigenic than are the parent substances, are employed for the production of whole culture vaccines.

INFLUENZA VIRUS VACCINE, POLYVALENT.—Polyvalent influenza virus vaccine is a sterile suspension of formaldehyde-killed influenza viruses, types A, A prime and B. The vaccine contains types A, A prime and B viruses recovered from the extra-embryonic fluids—preferably from the allantoic fluid only—of chick embryos infected with these viruses. The A, A prime and B components are serologically different. Since present knowledge is inadequate with respect to the strains required to provide a vaccine having complete antigenic coverage, the vaccine contains only those strains of the viruses designated by the National Institutes of Health. The product complies with the official potency test and other requirements of the National Institutes of Health of the United States Public Health Service.

Actions and Uses.—Polyvalent influenza virus vaccine is used prophylactically for active immunization against the component strains of influenza viruses. Subcutaneous administration of the vaccine stimulates production of antibodies which appear in the serum approximately a week after injection, reach maximum titers during the second week, remain constant for approximately a month and then decline gradually. The duration of protection following vaccination still is under discussion, because resistance to infection varies widely among individuals. Since the vaccine is prepared with so few strains of the two serologic types of virus, it will not protect against all strains. Administration of the vaccine to individuals with established infections with these viruses is not rational and may lead to increased symptoms.

The vaccine may cause toxic symptoms, particularly in children because of the high concentration of the inactivated viruses. The vaccine should not be used in persons sensitive to material derived from chick or egg protein.

Dosage.—Usual, hypodermic, for prophylactic active immunization, a single dose: 1 cc for adults, 0.5 cc or less for children under 12 years of age. A second injection may be indicated in epidemics of influenza virus infections.

LEIBERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

Influenza Virus Vaccine, Polyvalent 1 cc vials (one immunization) and 10 cc vials (ten immunizations). Preserved with thimerosal 1:10,000.

ELI LILLY & COMPANY

Influenza Virus Vaccine, Polyvalent 1 and 5 cc vials. Preserved with thimerosal 1:10,000.

THE NATIONAL DRUG COMPANY

Influenza Virus Vaccine, Polyvalent 1 and 5 cc vials. Preserved with thimerosal 1:10,000.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

Influenza Virus Vaccine, Polyvalent 1 cc vials (one immunization) and 5 cc vials (five immunizations). Preserved with thimerosal 1:10,000.

SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Influenza Virus Vaccine, Polyvalent, Protamine Concentrated and Refined: 1 and 10 cc. vials. Preserved with thimerosal 1:10,000.
U. S. patent 2,445,301.

PERTUSSIS VACCINE-U.S.P.—Whooping Cough Vaccine.—"Pertussis Vaccine is a sterile bacterial fraction or suspension, in an isotonic sodium chloride solution or other suitable diluent, of killed pertussis bacilli (*Hemophilus pertussis*) of a strain or strains selected for high antigenic efficiency. It has a potency of not less than 4 protective units per individual immunizing dose based on the N.I.H. Standard Pertussis Vaccine. It contains a suitable antibacterial agent approved by the National Institutes of Health."
U.S.P.

Physical Properties.—Pertussis vaccine is a more or less turbid, whitish liquid, nearly odorless or having a faint odor caused by the preservative.

Actions and Uses.—Well controlled field studies indicate that pertussis vaccine possess considerable protection against the death rate is ever attacks of the disease
jection of vaccine. Such cases usually are less severe.

Encephalopathic symptoms occasionally occur with whooping cough and, more rarely, with the use of the prophylactic vaccine. Such severe symptoms of the central nervous system have included convulsions and lethargy. These may be followed by mental death.
units,
oses of

CUTTER LABORATORIES

Pertussis Vaccine: 1.5 cc. (one immunization: three 0.5 cc. injections), 7.5 cc. (five immunizations) and 15 cc. vials (ten immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

ELI LILLY & COMPANY

Pertussis Vaccine: 7.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000

THE NATIONAL DRUG COMPANY

Pertussis Vaccine: 1.5 cc. (one immunization: three 0.5 cc. injections) and 7.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

PARKE, DAVIS & COMPANY

Pertussis Vaccine: 1.5 cc. (one immunization) and 7.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with 0.01 per cent merthiolate.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

Pertussis Vaccine: 20 cc. vials (five immunizations: three injections of 1, 1.5 and 1.5 cc.). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000

SHERMAN LABORATORIES

Pertussis Vaccine: 12.5 cc vials (three immunizations) and 20 cc. vials (five immunizations) Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

U. S. STANDARD PRODUCTS COMPANY

Pertussis Vaccine: 7.5 cc. (five immunizations) and 22.5 cc. vials (fifteen immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

WYETH LABORATORIES, INC.

Pertussis Vaccine: 7.5 cc vials (five immunizations) Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 0.01 per cent

not less than 4 protective units per individual immunizing dose based on the N.I.H. Standard Pertussis Vaccine. It contains a suitable antibacterial agent approved by the National Institutes of Health, and not more than 15 mg. of alum in the volume stated in the labeling to constitute one injection "U.S.P."

Physical Properties.—Alum precipitated pertussis vaccine is a turbid, whitish liquid. It is essentially odorless. It must be free from harmful substances detectable by animal inoculation and must not contain an excessive proportion of preservative.

Actions and Uses.—See the monograph on pertussis vaccine. Because of the physical character of the alum precipitated product, absorption is delayed.

Dosage.—The usual hypodermic dose, for active immunization, is 1.5 cc. (12 units, N.I.H.), divided into not less than three individual injections with intervals of 4 to 6 weeks between injections. It is desirable to give a booster dose (0.5 cc.) 1 year after primary immunization and again at school age.

ELI LILLY & COMPANY

Pertussis Vaccine (Alum Precipitated): 1.5 cc. (one immunization) and 7.5 cc vials (five immunizations) Total immunizing dose contains 12 units of pertussis vaccine. Preserved with 0.01 per cent thimerosal.

THE NATIONAL DRUG COMPANY

Pertussis Vaccine (Alum Precipitated): One 0.5 cc. vial (supplementary dose). Preserved with thimerosal 1:10,000. For use as a booster dose to maintain a high protective level.

Pertussis Vaccine (Alum Precipitated): 7.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

Pertussis Vaccine, Alum Precipitated: 5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:7,500.

PERTUSSIS VACCINE, ALUMINUM HYDROXIDE ADSORBED.—Aluminum hydroxide adsorbed pertussis vaccine is a sterile suspension in a suitable diluent of killed pertussis bacilli (*Hemophilus*

other requirements of the National Institutes of Health of the United States Public Health Service.

Actions and Uses.—See the monograph on pertussis vaccine. Because of the physical character of the aluminum hydroxide adsorbed product, absorption is delayed.

Dosage.—For active immunization, a total of 1.5 cc (12 units, N.I.H.) is administered hypodermically, divided into not less than three individual injections, with intervals of 4 to 6 weeks between injections.

CUTTER LABORATORIES

Pertussis Vaccine, Aluminum Hydroxide Adsorbed (Alhydrox): 7.5 cc vials (five immunizations—three 0.5 cc. injections for each). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

COMBINATIONS OF VACCINES AND TOXOIDS

These combinations of active immunizing agents are advantageous in reducing the number of immunization procedures required for immunity against several infectious diseases and in providing a synergistic effect which enhances and increases production of antibodies for each component of the product.

There is some evidence that it is advisable not to perform routine elective immunization with these preparations (or their components) in the summer and early fall, when the incidence of anterior poliomyelitis is high (*J.A.M.A.* 144:259 [Sept. 16], 1950)

DIPHTHERIA TOXOID AND PERTUSSIS VACCINE COMBINED. N.F.—**Diphtheria (CUTTER)**—"Diphtheria Toxoid and Pertussis Vaccine Combined is a sterile mixture of Diphtheria Toxoid and Pertussis Vaccine combined in such proportion as to yield a mixture containing an immunizing dose of each in the total dosage prescribed on the label. Diphtheria Toxoid and Pertussis Vaccine Combined complies with the official potency tests and other requirements of the National Institutes of Health of the United States Public Health Service" *N.F.*

Physical Properties.—Diphtheria toxoid and pertussis vaccine combined is a more or less turbid, whitish liquid. It is nearly odorless. It must be free from harmful substances detectable by animal inoculation and must not contain an excessive proportion of preservative.

Actions and Uses.—Employed in the simultaneous immunization against diphtheria and whooping cough.

Dosage.—Usual, hypodermic, for active immunization, 3 injections of 0.5 or 1 cc., whichever is specified on the label, every 3 to 4 weeks representing the NF dosage of diphtheria toxoid and pertussis vaccine.

CUTTER LABORATORIES

Diphtheria: 1.5 cc (one immunization) three 0.5 cc injections and 7.5 cc vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

DIPHTHERIA TOXOID AND PERTUSSIS VACCINE COMBINED, ALUM PRECIPITATED.—Alum precipitated diphtheria toxoid and pertussis vaccine combined is a sterile mixture of diphtheria toxoid and pertussis vaccine precipitated with alum and combined in such proportion as to yield a mixture containing an immunizing dose of each in the total dosage prescribed on the label. Alum precipitated diphtheria toxoid and pertussis vaccine combined complies with the official potency tests and the requirements of the National Institutes of Health of the United States Public Health Service.

Actions and Uses.—See the monograph on diphtheria toxoid and pertussis vaccine combined. Because of the physical character of the alum precipitated product, absorption is delayed.

Dosage.—Usual, hypodermic, for active immunization, not less than three repeated injections representing the USP dosage for diphtheria toxoid alum precipitated and for pertussis vaccine alum precipitated.

THE NATIONAL DRUG COMPANY

Diphtheria Toxoid, Alum Precipitated and Pertussis Vaccine Combined. Three 0.5 cc vials (one immunization) and three 2.5 cc vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine with diphtheria toxoid. Preserved with thimerosal 1:10,000.

FITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

Diphtheria Toxoid, Alum Precipitated and Pertussis Vaccine Combined. 4.5 cc vials (three immunizations) three 0.5 cc injections. Total immunizing dose contains 12 units of pertussis vaccine with diphtheria toxoid. Preserved with thimerosal 1:10,000.

DIPHTHERIA TOXOID AND PERTUSSIS VACCINE COMBINED, ALUMINUM HYDROXIDE ADSORBED.—**Diphtheria.** Alhydrox (Cutter). Aluminum hydroxide adsorbed diphtheria toxoid and pertussis vaccine combined is a sterile mixture of diphtheria toxoid and pertussis vaccine, adsorbed on aluminum hydroxide and com-

bined in such proportion as to yield a mixture containing an immunizing dose of each in the total dosage prescribed on the label. Aluminum hydroxide adsorbed diphtheria toxoid and pertussis vaccine combined complies with the official potency tests and other requirements of the National Institutes of Health of the United States Public Health Service.

Actions and Uses.—See the monograph on diphtheria toxoid and pertussis vaccine combined. Because of the physical character of the aluminum hydroxide adsorbed product, absorption is delayed.

Dosage.—Usual, hypodermic, for active immunization, not less than three repeated injections representing the U.S.P. dosage for diphtheria toxoid, aluminum hydroxide adsorbed and for pertussis vaccine, aluminum hydroxide adsorbed.

CUTTER LABORATORIES

Diptussis, Alhydrox: 1.5 cc. (one immunization, three 0.5 injections) and 7.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine with diphtheria toxoid. Preserved with thimerosal 1:10,000.

Combined Diphtheria and Tetanus Toxoids with Pertussis Vaccine (Tridipigen).—Tridipigen (Lilly). Combined diphtheria and tetanus toxoids with pertussis vaccine is a sterile mixture of diphtheria toxoid, tetanus toxoid and pertussis vaccine combined in such proportion as to yield a mixture containing an immunizing dose of each in the total dosage prescribed on the label.

Combined diphtheria and tetanus toxoids with pertussis vaccine complies with the official potency tests and other requirements of the National Institutes of Health of the United States Public Health Service.

Actions and Uses.—Employed in the simultaneous active immunization of susceptible persons against diphtheria, tetanus and whooping cough.

Dosage.—Usual, hypodermic, for active immunization, not less than three divided doses, administered at intervals of 3 or 4 weeks, the total being at least the U.S.P. immunizing doses of diphtheria toxoid, tetanus toxoid and pertussis vaccine.

CUTTER LABORATORIES

Dip-Pert-Tet: 1.5 cc. (one immunization: three 0.5 cc. injections), 7.5 cc. (five immunizations) and 22.5 cc. vials (fifteen immunizations). Total immunizing dose contains 12 units of pertussis vaccine with diphtheria and tetanus toxoids. Preserved with thimerosal 1:10,000.

ELI LILLY & COMPANY

Tridipigen (Fluid): 1.5 cc vials (one immunization) and 7.5 cc vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine with diphtheria and tetanus toxoids. Preserved with thimerosal 1:10,000.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Combined: 1.5 cc. (one immunization: three 0.5 cc. injections) and 7.5 cc. vials (five immunizations) Total immunizing dose contains 12 units of pertussis vaccine with diphtheria and tetanus toxoids Preserved with thimerosal 1 10,000.

U. S. STANDARD PRODUCTS COMPANY

Diphtheria and Tetanus Toxoids with Pertussis Vaccine, Combined: 1.5 cc (one three-dose immunization), 7.5 cc (five three-dose immunizations) and 22.5 cc (fifteen three-dose immunizations) vials Total immunizing dose contains 12 units of pertussis vaccine with diphtheria and tetanus toxoids Preserved with thimerosal 1 10,000

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE COMBINED, ALUM PRECIPITATED-U.S.P.—Infagen (PITMAN-MOORE)—Tridipigen (LILLY)—Trisavac (SHARP & DOHME)—"Alum Precipitated Diphtheria and Tetanus Toxoids and Pertussis Vaccine Combined is a sterile suspension of the precipitate obtained by treating a mixture of diphtheria toxoid, tetanus toxoid, and pertussis vaccine with alum, and combined in such proportion as to yield a mixture containing an immunizing dose of each in the total dosage prescribed on the label It contains a suitable antibacterial agent approved by the National Institutes of Health, and not more than 15 mg. of alum in the volume stated in the labeling to constitute one injection" U.S.P.

Physical Properties.—Alum precipitated diphtheria and tetanus toxoids and pertussis vaccine combined is a markedly turbid, whitish liquid It is nearly odorless or has a faint odor caused by the preservative

Actions and Uses.—See the monograph on diphtheria and tetanus toxoids with pertussis vaccine combined Because of the physical character of the alum precipitated product, absorption is delayed

Dosage.—Usual, hypodermic, for active immunization, three injections of 0.5 or 1 cc., as specified in the labeling, administered at intervals of 3 to 4 weeks

ELI LILLY & COMPANY

Tridipigen, Alum Precipitated: 1.5 cc (one three-dose immunization) and 7.5 cc vials (five three-dose immunizations) One three-dose immunization provides a complete immunizing course of diphtheria and tetanus toxoids and 12 units of pertussis vaccine. Preserved with thimerosal 1 10,000

THE NATIONAL DRUG COMPANY

Diphtheria and Tetanus Toxoids Alum Precipitated, and Pertussis Vaccine Combined: Three 0.5 cc vials (one immunization), three 2.5 cc vials and one 7.5 cc vial (five immunizations) One complete immunizing treatment of three 0.5 cc injections contains two

human doses each of diphtheria and tetanus toxoids and 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC

Infagen: 75 cc vials (five immunizations: three 0.5 cc. injections) Total immunizing dose contains 12 units of pertussis vaccine with diphtheria and tetanus toxoids. Preserved with thimerosal 1:10,000.

SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Trinavac, Alum Precipitated: One 1.5 cc. vial (one three-dose immunization) and one 75 cc. vial (five three-dose immunizations). One three-dose immunization provides a complete immunizing course of diphtheria and tetanus toxoids and 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

U S patents 2,528,972 and 2,584,093 U S trademark 598,096

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Diphtheria and Tetanus Toxoids Alum Precipitated and Pertussis Vaccine Combined: 75 cc. vials (five three-dose immunizations). One three-dose immunization provides a complete immunizing course of diphtheria and tetanus toxoids and 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

U. S. STANDARD PRODUCTS COMPANY

Aquagen Diphtheria and Tetanus Toxoids and Pertussis Vaccine Combined, Alum Precipitated: 15 cc (one three-dose immunization) and 75 cc (five three-dose immunizations) vials. One three-dose immunization provides a complete immunizing course of diphtheria and tetanus toxoids and 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE COMBINED, ALUMINUM HYDROXIDE ADSORBED-U.S.P.—Dip-Pert-Tet, Alhydrox (CUTTER)—"Aluminum Hydroxide Adsorbed Diphtheria and Tetanus Toxoids and Pertussis Vaccine Combined is a sterile mixture of diphtheria toxoid, tetanus toxoid, and pertussis vaccine, adsorbed on aluminum hydroxide. The antigens are combined in such proportion as to yield a mixture containing one immunizing dose of each in the total dosage prescribed on the label. It contains a suitable antibacterial agent approved by the National Institutes of Health, and not more than 0.85 mg. of aluminum in the volume stated in the labeling to constitute one injection" U.S.P.

Physical Properties.—Aluminum hydroxide adsorbed diphtheria and tetanus toxoids and pertussis vaccine combined is a markedly turbid, whitish liquid. It is nearly odorless or has a faint odor caused by the preservative.

Actions and Uses.—See the monograph on diphtheria and tetanus toxoids with pertussis vaccine combined. Because of the physical

character of the aluminum hydroxide adsorbed product, absorption is delayed.

Dosage.—Usual, hypodermic, for active immunization, three injections of 0.5 or 1 cc, as specified in the labeling, at intervals of 3 to 4 weeks

CUTTER LABORATORIES

Dip-Port-Tet, Alhydrox 1.5 cc (one immunization, three 0.5 cc. injections) and 7.5 cc vials (five immunizations) Total immunizing dose contains 12 units of pertussis vaccine with diphtheria and tetanus toxoids Preserved with thimerosal 1:10,000

AGENTS FOR CUTANEOUS IMMUNITY TESTS

In the armamentarium of preventive medicine, tests for susceptibility to infectious diseases are of great value Mass immunization programs which prevent epidemics often are based on evidence that a population is susceptible to a given infection

Modern medicine relies less on tests for susceptibility than formerly was the case, the physician prefers "routine elective" immunization instead when specific immune agents are available

The tuberculins, diphtheria toxin and scarlet fever streptococcus toxin (Dick test) are agents for testing susceptibility to specific micro-organisms

A positive tuberculin test, irrespective of the testing method, merely indicates the presence of allergy or hypersensitivity to tuberculin and that the individual is infected or has been infected with tubercle bacilli A negative tuberculin reaction to the strongest concentration used in testing definitely indicates the absence of tuberculin allergy but does not eliminate the possibility of tuberculous infection in individuals whose skin has become anergic (without allergic reactivity) In rare instances, convalescence from acute infectious disease, anesthesia, early tuberculosis, senility, severe malnutrition and various other conditions may interfere with the test and a false negative tuberculin reaction may be obtained Tuberculins formerly were used in the therapy of tuberculosis but in recent years they have been superseded by antibiotics and other chemotherapeutic agents

Differential diagnoses can be made by employing certain immunologic agents, such as the streptococcus antitoxin in the Schulte Charlton test, for cutaneous reactions

Tests for Susceptibility

PURIFIED PROTEIN DERIVATIVE OF TUBERCULIN U.S.P.—Tuberculin PPD—"Purified Protein Derivative of Tuberculin is a sterile, soluble purified product of growth of the tubercle bacillus (*Mycobacterium tuberculosis*) prepared in a special liquid medium free from protein" U.S.P.

Physical Properties—Purified protein derivative of tuberculin is a whitish amorphous powder readily soluble in water It is supplied usually in tablet form

Actions, Uses and Dosage.—Purified protein derivative of tuberculin is used for the diagnosis of tuberculosis by intracutaneous injection (Mantoux test). A positive local reaction merely indicates that the patient has been infected with tuberculosis at some time, not necessarily that he has clinical tuberculosis at the time of the test. It indicates, however, complete study of the patient since it is presumptive evidence that tubercle bacilli are, or have been, present.

Standard doses of 0.00002 mg. and 0.0002 mg. of purified protein derivative of tuberculin are used. The second dose should not be used until the first has been found to give a negative reaction. It is marketed in the form of tablets containing these amounts, with a vial of diluent for making freshly prepared solutions. Best results require that the solutions thus prepared be used immediately even though they are somewhat more stable than old tuberculin.

The reaction is determined after 48 hours. If this is negative after a dose of 0.00002 mg., a second dose of 0.0002 mg. should be injected into the opposite arm. If, after 48 hours, no reaction appears, a dose of 0.002 may be injected, but in routine testing of presumably nontuberculous children, the test rarely is carried thus far. The

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culosis, even for nonpulmonary infections, has been largely abandoned as it is capable of harm.

PARKE, DAVIS & COMPANY

Tablets Tuberculin, Purified Protein Derivative (First Strength): Packages containing 2 vials (5 tests each) and 1 cc. vial of sterile diluent; and packages containing 10 tablets (100 tests) with 10 cc. vial of diluent.

Tablets Tuberculin, Purified Protein Derivative (Second Strength): Packages containing 2 vials (5 tests each) and 1 cc. vial of sterile diluent; and packages containing 10 tablets (100 tests) with 10 cc. vial of diluent.

Agents Used in Metabolic Disorders

This chapter describes four groups of substances used in the treatment of metabolic disorders: (1) Substances that have a special influence on metabolism, such as thiouracil and derivatives which affect the activity of the thyroid gland, (2) substances that are administered in order that they themselves may be metabolized, such as dextrose, amino acids, salts of calcium, certain compounds of iodine and lipotropic agents, (3) substances used in the replacement of extracellular electrolytes following dehydration and acidosis, and (4) substances used to reduce the concentration of extracellular electrolytes.

Compounds employed only as contrast media for roentgenography or other diagnostic procedures will be found in the chapter on diagnostic aids. Insulin and thyroid preparations, important as metabolic agents, are classified with endocrine substances in the chapter on hormones and synthetic substitutes.

PROTEIN HYDROLYSATES AND AMINO ACID PREPARATIONS

A number of protein hydrolysate preparations, prepared from suitable proteins by acid or enzyme digestion, are of value in intravenous feeding. Since these products are administered in large quantities directly into the blood stream, their preparation involves the careful control required of all intravenous preparations. Other or similar preparations of protein hydrolysates in powder form suitable for oral feeding also have been available and are recommended for use in supplementing the diets of infants and children who may be allergic to protein in the diet, or of older persons for whom a high protein intake is desirable.

Preparations of individual amino acids also have been available for the treatment of certain specific conditions. Aminoacetic acid (glycine), formerly used in the treatment of myasthenia gravis, and histidine, which has been tried for the treatment of peptic ulcer, are examples. Neither of these is recognized currently to be of specific value in these conditions, nor has methionine or lysine been established definitely to be of specific therapeutic value in treating liver disease.

The primary purpose of amino acid mixtures or protein hydrolysates, whether administered intravenously or orally, is to supply dietary nitrogen in readily assimilable form when there is

serious interference with intake, digestion or absorption of dietary protein. Evidence is lacking to indicate that the addition of amino acids to foods will accomplish anything that cannot be accomplished by proper use of proteins as they occur naturally in the diet when there is no such interference. Products containing amino acids combined with vitamins and minerals in tablet and elixir form have appeared on the market. Such tablets or elixirs supply amounts of amino acids insufficient for rational use in human nutrition.

The amino acids that are indispensable for protein synthesis in adult man comprise those which the body itself is unable to synthesize. The minimum quantities of these acids needed daily to maintain nitrogen balance in the healthy adult human being are as follows. tryptophan, 0.25 Gm; phenylalanine, 1.1 Gm; lysine, 0.8 Gm.; threonine, 0.5 Gm; valine, 0.8 Gm.; methionine, 1.1 Gm; leucine, 1.1 Gm; isoleucine, 0.7 Gm. These eight amino acids must be provided in mixtures intended for protein replacement in man. Such preparations provide additional amino acids, which are found as component parts of tissue and body protein, but usually are termed "nonessential" because they can be synthesized by the body from other substances.

Nitrogen balance studies have shown that the average amount of protein required to maintain nitrogen equilibrium in the adult on a mixed diet is about 45 Gm daily, with wide individual variation related, in part, to the variations in biologic value of the total protein in the diet. To allow for these variations, 70 Gm of protein ordinarily is regarded as the recommended daily intake.

The Council considers useful for oral or intravenous administration only protein hydrolysates of biologically adequate proteins (such as casein) or proteins that are obtained from suitable sources (such as blood) that have been hydrolyzed to the extent that at least 50 per cent of the total nitrogen present is in the form of alpha amino nitrogen. This minimum degree of hydrolysis is essential to justify the designation of such products as hydrolysates and to ensure their nonantigenicity. To promote nitrogen retention and growth in infants and children, who may be allergic to dietary protein and are fed hydrolysates as substitutes for protein, it is required that all essential amino acids be in the protein hydrolysate in adequate amounts and that growth in experimental animals limited to the hydrolysate as the only source of nitrogen should be demonstrated adequately.

PROTEIN HYDROLYSATES (INTRAVENOUS)—PROTEIN HYDROLYSATE INJECTION—U S P—Amigen (MEAD JOHNSON)—Aminosol (ABBOTT)—Hyprotigen (DON BAXTER)—Paranamine (WINTHROP-STEARNS)—Travamin (BAXTER).—"Protein Hydrolysate Injection is a sterile solution of amino acids and short-chain peptides which represent the approximate nutritive equivalent of the casein, lactalbumin, plasma, fibrin, or other suitable protein from which it is derived by acid, enzymatic, or other method of hydrolysis. It may be modified by partial removal and restoration or addition of one or more amino acids. It may contain dextrose

or other carbohydrate suitable for intravenous infusion. Not less than 50 per cent of the total nitrogen present is in the form of α -amino nitrogen." *U.S.P.*

Protein cannot supply calories and at the same time contribute to body protein synthesis. The purpose of dextrose is to provide a source of calories, and it should be recognized that hydrolyzed protein will not be used efficiently for body protein synthesis unless adequate nonprotein calories are made available, preferably simultaneously. Although in calculating the caloric value of foods it is common practice to use the value of 4 calories per gram for carbohydrates and proteins, the physician may need a more accurate evaluation for injectable protein hydrolysates used for intravenous feeding. Dextrose, most frequently used in these solutions, is the monohydrate, and, therefore, provides 3.4 calories per gram. When protein is hydrolyzed the resultant amino acid mixture provides about 3.5 calories per gram instead of the 4 calories per gram available from protein. Thus a 5 per cent protein hydrolysate solution will provide 175 calories per liter, and a similar solution containing 5 per cent dextrose will supply 345 calories per liter.

Actions and Uses.—Parenteral preparations of protein hydrolysates are useful for the maintenance of positive nitrogen balance in conditions in which there is interference with ingestion, digestion or absorption of food. These conditions are encountered most frequently in severe illness and after surgical operations involving the alimentary tract. The usefulness of hydrolysates is limited when the patient's caloric supply is inadequate and, for tissue synthesis, their utilization varies directly with the caloric intake. This may not apply when patients have severe protein depletion and when it is important to reduce nitrogen loss. In the acute "catabolic" phase of nitrogen loss in healthy persons who suddenly become ill, it may be extremely difficult to achieve nitrogen balance with the amount of hydrolysate that can be administered. The acute nitrogen loss of brief severe illness has not been shown to be pernicious and it is debatable whether hydrolysates should be employed under these circumstances. Protein hydrolysates should not be administered as a substitute for food proteins if the latter can be utilized adequately.

Intravenous injection is contraindicated during acidosis. Injection may produce untoward effects such as nausea, vomiting, vasodilatation, abdominal pain, convulsions, edema at the site of injection, phlebitis and thrombosis. Care must be exercised to prevent reactions that indicate danger. Many unfavorable reactions have been traced to inadequate care in the cleanliness of equipment, and to too rapid administration. The manufacturers' instructions for administration should be followed closely. Solutions that are cloudy, contain sediment or have been opened for a previous injection should not be used. Unopened solutions should be stored in a cool place.

Dosage.—See the general statement on protein hydrolysates and amino acid preparations. Dosage is determined by the physician, taking into consideration the age, weight and nutritional status of the patient, with respect to protein, caloric, fluid and electrolyte

requirements. The average protein requirement for adults is about 1 Gm. per kilogram of body weight per day. In calculating the effective dosage, account should be taken of urinary loss. The amount of loss is difficult to predict and will depend upon such variables as caloric intake, rate of infusion and character of the hydrolysate.

ABBOTT LABORATORIES

Solution Aminosol 5%: 500 and 1,000 cc. Abbo-Liter bottles. A 5 per cent modified fibrin hydrolysate. A solution containing 5 Gm. of protein hydrolysate equivalent to about 17 calories, 66 mg. of potassium ion and less than 23 mg. of sodium ion in each 100 cc.

Solution Aminosol 5% with Dextrose 5%: 250, 500 and 1,000 cc. Abbo-Liter bottles. A 5 per cent modified fibrin hydrolysate with 5 per cent dextrose. A solution containing 5 Gm. of protein hydrolysate and 5 Gm. carbohydrate equivalent to about 34.5 calories, 66 mg. of potassium ion and less than 23 mg. of sodium ion in each 100 cc.

Solution Aminosol 5% with Dextrose 5% and Sodium Chloride 0.3%: 1,000 cc. Abbo-Liter bottles. A 5 per cent modified fibrin hydrolysate. A solution containing 5 Gm. of protein hydrolysate and 5 Gm. of carbohydrate equivalent to about 34.5 calories and 66 mg. of potassium ion in each 100 cc.

U. S. trademark 414,539.

DON BAXTER, INC.

Solution Hyprotigen 6%: 500 and 1,000 cc. bottles. An enzymatic hydrolysate of casein containing amino acids and polypeptides. It contains approximately 55 per cent of its total nitrogen as alpha amino nitrogen.

Solution Hyprotigen 6% with Dextrose 5%: 500 and 1,000 cc. bottles. An enzymatic hydrolysate of casein containing amino acids and polypeptides with added dextrose. It contains approximately 55 per cent of its total nitrogen as alpha amino nitrogen.

U. S. trademark 434,994.

BAXTER LABORATORIES, INC.

Solution Travamin 5%: 500 cc and 1 liter bottles. A solution containing 50 mg. of enzymatic hydrolysate of bovine plasma in each cubic centimeter. Fifty per cent of the total nitrogen is present as alpha amino nitrogen.

Solution Travamin 5% with Dextrose 5%: 150 and 500 cc. and

U. S. trademark 533,766

MEAD JOHNSON & COMPANY

Solution Amigen 3.33% with Dextrose in Lactated Ringer's Solution (Diluted 1:3): 250 cc. bottles. Each 100 cc. contains 3.33 Gm of protein hydrolysate and 3.33 Gm. of dextrose in lactated Ringer's solution (diluted 1:3).

Solution Amigen 5% with Dextrose 5%: Bottles of 125, 500 and 1,000 cc. Each 100 cc contains 5 Gm of protein hydrolysate and 5 Gm. of dextrose.

Solution Amigen 5% with Dextrose 10%: 1 liter bottles Each 100 cc. contains 5 Gm of protein hydrolysate and 10 Gm. of dextrose.

Solution Amigen 5% with Levugen 10%: 1,000 cc bottles Each 100 cc contains 5 Gm of protein hydrolysate and 10 Gm of fructose.

Solution Amigen 10%: 500 cc. bottles. Each 100 cc. contains 10 Gm. of protein hydrolysate

U. S. patent 2,180,637. U. S. trademarks 381,523, 387,310 and 422,992.

WINTHROP-STEARNs, INC.

Solution Parenamino 6%: 1,000 cc bottles A solution containing 6 Gm. of casein hydrolysate equivalent to 21 calories in each 100 cc. The preparation consists essentially of amino acids prepared by acid hydrolysis.

Solution Parenamino 15%: 100 cc bottles A solution containing 15 Gm. of casein hydrolysate equivalent to 52.5 calories in each 100 cc. A preparation consisting essentially of amino acids which are prepared by acid digestion. Preserved with 0.05 per cent sodium bisulfite.

PROTEIN HYDROLYSATES (ORAL).—Aminonaf (NATIONAL).—Caminoids (ARLINGTON-FUNK)—Oral protein hydrolysate may be prepared from the same proteins or protein sources and are digested in the same manner and to the same extent as those for intravenous use. They are available in powdered form, flavored and unflavored. Their caloric value is calculated in the same manner as indicated under protein hydrolysates for intravenous use.

Actions and Uses.—Protein hydrolysate preparations that are of proved nutritional adequacy may be used orally in the diets of infants allergic to milk when the deficiency cannot be satisfactorily met by other foods, however, the hydrolysate must be combined suitably with other food ingredients before feeding as a formula. Protein hydrolysates also may supplement the diet when specific conditions require an especially high protein intake and when it is not feasible to accomplish this by ordinary foods. Any protein hydrolysate product that has proved effective for this purpose also may be employed as an adjunct in the management of peptic ulcer or other ulcerative conditions of the gastro-intestinal tract. Supplementing protein in other conditions is not recommended because

evidence is lacking to indicate the need for such supplementation. If the need should occur, it could be met by the use of ordinary foods.

Dosage.—See the monograph on protein hydrolysates for intravenous use.

ARLINGTON-FUNK LABORATORIES, DIVISION OF U. S. VITAMIN CORPORATION

Caminooids: 170.1 and 453.6 Gm., 2.27 and 4.54 Kg. containers. One tablespoonful (9 Gm) contains 4 Gm. of protein as partial hydrolysate. The powder contains about 3.5 calories per gram.

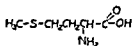
THE NATIONAL DRUG COMPANY

Powder Aminonut (Flavored): 2268 and 454 Gm. packages. A pancreatic digest of lactalbumin containing amino acids and polypeptides equivalent to about 87.5 per cent hydrolyzed protein providing 128 calories per 28.35 Gm. It has 61 per cent of its total nitrogen as amino nitrogen.

U. S. trademark 424,237.

Individual Amino Acids

METHIONINE-N.F.—Meonine (IVES-CAMERON).—Methione (LOBICA-DEBRUILLE).—DL-Methionine.— α -Amino- γ -methylmercaptobutyric acid—"Methionine, dried at 105° for 4 hours, contains not less than 98 per cent of $C_5H_{11}NO_2S$," N.F. The structural formula of methionine may be represented as follows.



Physical Properties.—Methionine forms white, crystalline platelets or is a powder. It has a faint odor. It is soluble in water, dilute acids and dilute alkalis, very slightly soluble in alcohol and practically insoluble in ether. A 1 per cent aqueous solution of methionine has a pH between 5.6 and 6.1.

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liver disease for those patients who cannot take an adequate diet. However, in patients with severe liver damage large doses may exaggerate the toxemia of the disease. Studies with experimental animals indicate a need for caution in administering this amino acid in its free form even though it is recognized as an essential nutrient and can be consumed in great excess when combined in proteins without adverse effect.

Dosage—As a supplement to a high protein diet, 3 to 6 Gm. is usually administered daily in tablet or capsule form.

ABBOTT LABORATORIES

Tablets Methionine: 0.5 Gm.

IVES-CAMERON COMPANY, DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Tablets Meonine: 0.5 Gm.

U. S. trademark 406,590.

LOBICA-DEBRVILLE, INC.

Powder Metione (Flavored): 2 Gm. envelopes. A powder containing in each pliofilm envelope 1.6 Gm. of DL-methionine, 0.16 Gm. of lactose, 0.16 Gm. of sugar and 0.08 Gm. of coffee.

TABLEROCK LABORATORIES

Tablets Methionine: 0.5 Gm.

U. S. VITAMIN CORPORATION

Capsules Methionine: 0.5 Gm.

WALKER LABORATORIES, INC.

Capsules Methionine: 0.5 Gm.

ANTITHYROID DRUGS

IOTHIOURACIL SODIUM—Itrumil Sodium (CIBA)—Sodium 5-iodo-2-thiouracil—The structural formula of iothiouracil sodium may be represented as follows:



Physical Properties.—Iothiouracil sodium is an odorless, white to light yellow, crystalline powder, with a melting point between 235 and 240° (with decomposition). The approximate amounts that dissolve at 25° in the following solvents to form 100 cc. of solution are: 0.5 Gm. in alcohol and 3.5 Gm. in water. It is practically insoluble in acids. Iothiouracil sodium usually is obtained as the dihydrate which is reasonably stable to moisture and sunlight at room temperature. The pH of a 2 per cent solution is between 8.5 and 9.5.

Actions and Uses.—Iothiouracil sodium, an organic chemical iodine derivative of thiouracil, exhibits the thyroid-involuting effect of iodine and the antithyroid action (inhibition of thyroxin or thyroglobulin) of the parent drug. Iothiouracil sodium induces less thyroid vascularization and fewer goitrogenic effects (increased thyroid hyperplasia, gland size and friability) than non-iodinated thiouracil compounds. Although animal experiments indi-

cate that liothiouracil sodium is taken up more readily by the thyroid than noniodinated derivatives, clinical evidence so far obtained does not warrant the conclusion that the drug is superior to noniodinated derivatives administered concomitantly with iodine. Iothiouacil sodium is broken down in the body into its thiouracil and iodine portions, which are excreted separately.

Iothiouacil sodium is indicated in the preoperative management of hyperthyroidism, in the treatment of patients for whom thyroidectomy is contra-indicated and in the treatment of postoperative recurrent hyperthyroidism. It should be used with caution during pregnancy and should be discontinued during the last few weeks of pregnancy to prevent complications in the newborn; infants should not be nursed by mothers receiving therapy. It should be employed cautiously in persons known to be sensitive to iodine.

Like other thiouracil derivatives, liothiouracil sodium is associated with a lower incidence of toxic effects than the parent compound, thiouracil, but likewise may produce serious reactions that require cessation of medication. These include drug fever, skin rash, severe leukopenia, granulocytopenia and swelling of the cervical lymph nodes. A leukocyte and differential blood count should be made before treatment because of the frequent "spontaneous" appearance of leukopenia in hyperthyroidism; regular blood counts should be made during therapy and the patient instructed to report the appearance of any adverse symptoms.

Dosage.—Iothiouacil sodium is administered orally. In any given dose, iodine accounts for approximately 50 per cent, the thiouracil molecule for 40 per cent and the sodium ion for 10 per cent of the prescribed amount.

For preoperative management, an initial daily dosage of 0.15 to 0.2 Gm. (divided into doses of 50 mg. three or four times daily) may produce a satisfactory response in many patients, but most thyrotoxic patients require a daily dosage of 0.3 Gm. (0.1 Gm. three times daily) to produce rapid and complete remission. The established effective dosage for each patient should be continued until the disease has been controlled satisfactorily. For optimal preoperative results, from the standpoint of decreased vascularity and friability of the gland, at least 4 weeks of therapy is recommended; severely ill patients may not respond adequately until after 8 weeks. If a patient does not improve after a month of treatment at the minimum daily dosage level of 0.15 Gm., the dosage should be increased to 0.3 Gm. daily. If a second month of therapy at the higher dosage level fails to produce satisfactory response, the drug should be discontinued. Rarely, a daily dosage level of 0.6 to 0.8 Gm. may be instituted to control refractory patients.

For the treatment of patients in whom thyroidectomy is contra-indicated, or in instances of postoperative recurrence, the initially effective dosage may be reduced gradually to an adequate maintenance level. Therapy may be discontinued and resumed as required to keep the disease in check or to avoid untoward toxic effects; some patients cannot be kept in remission with continuous therapy.

CIBA PHARMACEUTICAL PRODUCTS, INC.

Tablets Irumil Sodium: 50 mg.

U. S. patent 2,585,615. U. S. trademark 564,371.

METHIMAZOLE-U.S.P.—Tapazole (LILLY)—1-Methyl-2-mercaptoimidazole.—“Methimazole, dried at 105° for 2 hours, contains not less than 98 per cent of $C_4H_6N_2S$.” U.S.P. The structural formula for methimazole may be represented as follows.



Physical Properties.—Methimazole is a white to buff, crystalline powder which has almost no taste and a very faint odor. It melts between 145 and 148°. One gram dissolves in about 4.5 cc. of water, in about 5 cc. of alcohol, in about 4.4 cc. of chloroform and in about 125 cc. of ether. A 2 per cent solution has a pH between 6.7 and 6.85.

Actions and Uses.—Methimazole is similar in indications and uses to propylthiouracil, but it is perhaps ten times as potent and its effect often is seen more readily. However, the action of the drug may be somewhat less consistent than that of propylthiouracil. The side effects also are similar to those of propylthiouracil and

may be expected to keep the disease under control.

ELI LILLY & COMPANY

Tablets Tapazole: 5 and 10 mg

METHYLTHIOURACIL-U.S.P.—Methiakil (SCHWARTZ).—Muracil (ORGANON)—Thimacil (PHYSICIANS' DRUG)—6-Methyl-2-thiouracil.—The structural formula of methylthiouracil may be represented as follows



Physical Properties.—Methylthiouracil is a white, odorless, crystalline powder. Methylthiouracil is very slightly soluble in ether and water, slightly soluble in alcohol and practically insoluble in

tially like those of propylthiouracil. There is a higher incidence of side reactions with this agent than with propylthiouracil or methimazole. It may prove useful in patients who are unable to tolerate or are refractory to other antithyroid drugs. See the monograph on propylthiouracil.

Dosage.—0.2 Gm daily in four divided doses usually is sufficient to control symptoms of hyperthyroidism. The daily dose should not exceed 0.3 Gm. It is recommended that the scheme of administration suggested for propylthiouracil be followed and the same precautions observed.

ORGANON, INC.

Tablets Muracil: 50 mg.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Thimecil: 50 mg

U. S. patent 505,850

SCHWARTZ LABORATORIES, INC.

Tablets Methiacil: 50 mg.

PROPYLTHIOURACIL-U.S.P. — 6-Propyl-2-thiouracil — "Propylthiouracil, dried at 103° for 2 hours, contains not less than 98 per cent of $C_7H_{10}N_2OS$." *U.S.P.* The structural formula of propylthiouracil may be represented as follows:



Physical Properties.—Propylthiouracil occurs as a white, powdery, crystalline substance. It is starchlike in appearance and to the touch and has a bitter taste. It is very slightly soluble in water. It is sparingly soluble in alcohol and is slightly soluble in chloroform and in ether. It is soluble in ammonia and in alkali hydroxides.

Actions and Uses.—Propylthiouracil is useful in the treatment of hyperthyroidism. It inhibits the oxidation of iodide ion stored in the thyroid gland, thus interfering with its ability to combine with tyrosine to form organic bound iodine, a precursor to the formation of thyroxine.

Since propylthiouracil does not inactivate or interfere with the action of thyroxine already formed and stored in the gland, the effects of propylthiouracil medication do not appear until this store of thyroxine has been utilized. It may take several days to several weeks for the signs of decreased thyroid activity to become manifest, particularly if the patient has received previous iodine therapy.

Not more than 50 per cent of patients on the average experience a permanent remission following propylthiouracil therapy, and the duration of treatment necessary to secure permanent relief from

hyperthyroidism may vary from 3 months to 3 years, averaging 1 year. Propylthiouracil may be used for preoperative treatment, for patients for whom operation is contraindicated and as a substitute for operative procedure.

In the preparation of patients for operation, propylthiouracil reduces the basal metabolic rate to a more nearly normal level than can be brought about by the use of iodine alone. The extreme vascularity and friability of the gland, encountered at operation following the preoperative administration of thiouracil derivatives alone, has been overcome by a longer period of preparation including concomitant administration of iodine for the last week prior to surgery. Propylthiouracil produces sustained effects and, thus, is not subject to the "escape" from its action that characterizes the use of iodine. Thus propylthiouracil provides more certain and constant control of hyperthyroidism so that the post-operative onset of thyroid "crisis" is less likely than when iodine is used alone.

Propylthiouracil is capable of producing adverse reactions in some patients. The incidence and severity of these reactions are unpredictable but their occurrence is less frequent than following medication with the parent compound, thiouracil. The most severe complication of propylthiouracil therapy is granulocytopenia. If this occurs the drug must be stopped immediately and penicillin administered to prevent the throat infections so common in this condition. Less severe reactions may include leukopenia, drug fever and dermatitis. The drug should be discontinued and appropriate therapy commenced immediately on the detection of signs of any of these complications.

Dosage—In hyperthyroidism an initial dose of 100 mg every 8 hours is effective in most cases. In some instances, and particularly in severe hyperthyroidism, as much as 600 mg daily in four to six doses may be required. The compound is metabolized rapidly, and, consequently, effective control requires frequent administration through the 24 hours.

The effective dose of propylthiouracil should be continued until all signs and symptoms of the disease have been brought under control. Adequate maintenance dosage may be established best by symptoms and clinical signs.

ABBOTT LABORATORIES

Tablets Propylthiouracil: 25 and 50 mg

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

Tablets Propylthiouracil: 25 and 50 mg

ELI LILLY & COMPANY

Tablets Propylthiouracil: 50 mg.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Propylthiouracil: 50 mg

RAYMER PHARMACAL COMPANY

Tablets Propylthiouracil: 50 mg.

REXALL DRUG COMPANY

Tablets Propylthiouracil: 50 mg.

THE UPJOHN COMPANY

Tablets Propylthiouracil: 50 mg.

SODIUM RADIO-IODIDE (131).—See the monograph in the chapter on radioactive isotopes.

CALCIUM COMPOUNDS

Calcium compounds are used therapeutically in overcoming calcium deficiency. The systemic action induced by calcium is dependent on the dosage and the mode of administration, which in turn vary with the calcium salt that is used. Relatively insoluble salts, if administered orally, are of little value. Soluble salts may be

ing to the etiology involved. In severe tetany, parenteral administration, preferably intravenous, is indicated to bring symptoms . . . rochloric

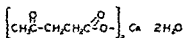
The chloride, lactate or carbonate salts of calcium are suitable for oral administration in doses corresponding to their calcium content. Persistent vomiting or the administration of large amounts of bicarbonate may cause tetany. Tribasic calcium phosphate has been administered orally when phosphorus as well as calcium is deficient, but its use probably should be restricted to less severe forms of calcium deficiency.

Intravenously injected overdoses may fatally paralyze the heart and the central nervous system. Intravenous injection should be made very slowly.

The therapeutic use of calcium in the absence of demonstrable . . . is irra-

CALCIUM LEVULINATE-N.F.—Calcium Levulinate is a hydrated

calcium salt of levulinic acid and contains not less than 97.5 per cent and not more than 100.5 per cent of $C_{10}H_{14}CaO_6$ calculated on a dry basis, the loss on drying being determined on a separate portion by drying in a vacuum oven at a pressure not exceeding 5 mm. and a temperature of 60° for 5 hours." *N.F.* The structural formula of calcium levulinate may be represented as follows:



Preparation.—Calcium levulinate occurs as a white, am-

form.

Actions and Uses.—Calcium levulinate produces the therapeutic effects of calcium. It may be administered orally or intravenously and is virtually nonirritant for subcutaneous or intramuscular injection.

Dosage.—By injection, for adults, 1 Gm. daily or on alternate days; for children, intravenously, 0.2 to 0.5 Gm. Orally, for adults, 4 to 5 Gm. three times a day; for children, 1 to 2 Gm. three times a day.

CHEMO PURO MANUFACTURING CORPORATION

Powder Calcium Levulinate: 30 and 480 Gm. bottles.

CHICAGO PHARMACAL COMPANY

Solution Calcium Levulinate: 10 cc. ampuls. A solution containing 0.1 Gm. of calcium levulinate in each cubic centimeter.

DIRECT LABORATORIES, INC.

Solution Calcium Levulinate: 10 cc. ampuls. A solution containing 0.1 Gm. of calcium levulinate in each cubic centimeter.

THE S. E. MASSENGILL COMPANY

Solution Calcium Levulinate: 10 cc. ampuls. A solution containing 0.1 Gm. of calcium levulinate in each cubic centimeter.

CARBACRYLAMINE RESINS

CARBACRYLAMINE RESINS.—Carbo-Resin (LILLY).—A mixture of 87.5 per cent of the cation exchangers, carbacrylic resin and potassium carbacrylic resin, and 12.5 per cent of the anion exchanger, polyamine-methylene resin. Two-thirds of the cation exchange mixture is carbacrylic resin (a polyacrylic carboxylic acid resin) and the remainder is the potassium salt of the carbacrylic resin.

Physical Properties.—Carbacrylamine resins is a light buff, free-flowing powder without appreciable odor. It is practically insoluble in dilute acids and alkalis, alcohol, ether and water. All of the

powder passes a 100-mesh screen and 75 per cent passes a 200-mesh screen.

Actions and Uses.—Carbacrylamine resins is used as an adjunct

chronic congestive heart failure, cirrhosis of the liver and the nephrotic syndrome.

The cation exchange resin is of the carboxylic acid type that gives up its hydrogen ions in exchange for cations. Its affinity for various cations differs in accordance with their valence and their order in the periodic table. Therefore, in a solution containing several

exchange capacity of the resin is utilized in the removal of that cation. It is estimated that in a man weighing 60 Kg. (132 lbs.), approximately 160 Gm of endogenous sodium enters the intestine every day along with the usual exogenous intake of 4 to 6 Gm. Some evidence indicates that the cation exchange resin acts chiefly on the exogenous sodium of the diet. Because of the capacity of the cation exchange resin to combine with other essential metallic ions, it has been found necessary to administer one-third of the resin as the potassium salt to prevent serum deficiency of that important cation. Carbacrylamine resins provides two-thirds of the cation exchange resin in the hydrogen form and one-third in the potassium form. The anion exchange resin makes up about one-eighth of the mixture and is added to reduce the tendency to acidosis produced by the cation exchange resin in patients with severe renal impairment caused by the inability of the kidney to manufacture sufficient ammonia. This tendency toward the production of acidosis is not obviated by the use of an ammonium salt in place of the hydrogen form of the carboxylic resin, since the ammonia that would be released is subsequently converted to urea in the liver. The anion exchange resin slightly increases the capacity of the cation exchange resin at the pH of the intestinal contents. Some investigators have observed that the cation exchange resin enhances the diuresis produced by mercurial diuretics. The use of the cation exchange resin is not intended to supplant the use of mercurial diuretics or dietary control of sodium intake. In edematous patients, who already exhibit a minimal urinary excretion of sodium prior to administration of the resin because of depletion of the body stores of sodium, there is little chance of producing a further reduction through the fecal diversion of dietary sodium.

Carbacrylamine resins must be employed with care to prevent the development of a low sodium syndrome, particularly in patients with an abnormal distribution of that electrolyte in the tissues. Precautions to guard against the development of acidosis also are essential. Periodic determinations of the carbon dioxide combining power and serum chlorides should be made when negative sodium balance has been present for some time after edema

has disappeared. Patients also should be observed regularly for signs of mineral deficiency in other cations, such as calcium. Since hyperkalemia can occur when urinary excretion is severely limited, the mixture should be used only in patients with adequate kidney function. Use of the potassium salt form as provided by the mixture is contraindicated for patients with anuria. Salt "substitutes" containing potassium should be used sparingly, if at all, because an increase in potassium intake may reduce the efficiency of the cation exchange resin. The mixture should not be employed without adequate laboratory facilities to follow the serum electrolyte pattern. Whenever food consumption is temporarily interrupted or sodium intake reduced, the dosage of the mixture must be adjusted accordingly. Large doses may produce gastro-intestinal discomfort, anorexia, nausea and vomiting, but care is needed to differentiate such symptoms from those caused by sodium depletion. The possibility of fecal impaction in elderly patients should be kept in mind.

Dosage.—Carbacrylamine resins is administered orally as a powder which can be dispersed in water. Each gram will remove approximately 1 milliequivalent (23 mg.) of sodium from the intestinal tract when the patient is on a diet containing at least 15 Gm. of sodium (37 Gm. of sodium chloride) per day. The number of metallic ions bound to the carboxylic resin decreases as the intake of salt is reduced. On a low sodium diet (0.5 Gm. or less), usually no more than 0.3 milliequivalent (7 mg.) of sodium is removed by each gram of the mixture. The total daily amount must be adjusted to meet the individual requirements of each patient. For patients with abnormal retention of sodium, who require restriction of sodium intake to 15 Gm. or less per day plus regular therapy with a mercurial diuretic, 48 Gm. of carbacrylamine resins usually is adequate to maintain an edema-free state when Gm. of with dif

suspended in 6 ounces of tap water or fruit juice, three times daily,

be increased. The maintenance dosage is adjusted on the basis of constant "dry" body weight when either the dietary intake of sodium can be increased or the total dose of the resin mixture reduced until body weight rises. The dosage required to maintain a balance between intake and output of sodium should be reduced by simultaneous moderate restriction of dietary sodium or by administration of a mercurial diuretic. In some persons severely restricted previously, the moderate increase of salt permitted with the administration of the resin mixture has been followed by in-

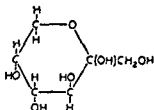
crease in appetite and nutrition. When edema fails to disappear during resin therapy, attention must be given to other factors that may participate in its etiology, such as hypoproteinemia.

ELI LILLY & COMPANY

Powder Carbo-Resin: 8 Gm packets and 450 Gm. bottles (flavored) and 450 Gm. bottles (unflavored). A mixture containing about 0.583 Gm. of carbacrylic resin, 0.292 Gm. of potassium carbacrylic resin and 0.125 Gm. of polyamine-methylene resin in each gram of powder.

CARBOHYDRATES

FRUCTOSE.—**Levugen** (MEAD JOHNSON).—**Levulose.**—**Fructose** is prepared by the inversion of aqueous solution of sucrose and subsequent separation of fructose from glucose. The structural formula of fructose may be represented as follows:



Physical Properties.—A 10 per cent solution is clear and colorless. The pH is 3.0 to 3.5.

Actions and Uses.—Fructose (levulose) like dextrose, administered intravenously in solution, is useful for parenteral carbohydrate alimentation when either fluid or calories are required to replace or supplement the oral consumption of water or food. When infused at comparable rates, it results in lower levels of blood sugar and less urinary spillage. Fructose is metabolized or converted to glycogen in the absence of insulin, but the clinical application of this has not been determined fully.

Fructose can be employed safely in the parenteral nutrition requirements of patients who are unable to take oral food, though fructose is not toxic, except in very large doses. Its use is contraindicated as with

Fructose is administered by intravenous infusion as a source of calories. The dose is determined on the basis of the size and total blood volume of the child. In infants this usually ranges from 0.1 to 1 liter and in children from 0.2 to 2 liters. If administered in quantities in excess of the amounts indicated, any unutilized portion will be excreted in the urine.

Since fructose decomposes in alkaline solution, substances which

would raise the pH to values above 7.0 should be added only if the solution is to be administered promptly. Compounds of calcium and barium form insoluble complexes when the pH exceeds 7.0 and, therefore, are incompatible. Cloudy solutions should not be used.

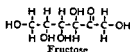
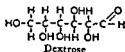
MEAD JOHNSON & COMPANY

Solution Levugen 10%: 1 liter bottles. A solution containing 0.1 Gm. of fructose in each cubic centimeter.

Solution Levugen 10% in Saline: 1 liter bottles. A solution containing 0.1 Gm. of fructose and 9 mg. of sodium chloride in each cubic centimeter.

Solution Levugen 10% with Electrolytes: 1 liter bottles. A solution containing 0.1 Gm. of fructose, 18 mg. of sodium chloride, 0.9 mg. of dibasic potassium phosphate and 0.4 mg. of potassium chloride in each cubic centimeter.

INVERT SUGAR—Travert (BAXTER).—An equimolecular mixture of dextrose and fructose (levulose) obtained by the inversion of sugar. The structural formulas for dextrose and fructose may be represented as follows.



Physical Properties.—Invert sugar solutions are clear and colorless. The solutions have a pH of 3.5 to 6.0.

Actions and Uses.—Invert sugar is used in place of dextrose for parenteral carbohydrate alimentation. Its caloric value, gram for gram, is identical with that of dextrose. When infused at comparable rates, it results in lower levels of blood sugar and less urinary spillage.

tions taken as with other forms of parenteral alimentation should be observed when administering invert sugar.

ABBOTT LABORATORIES

Solution Invert Sugar 5% in Water (or Saline): Abbo-Liter bottles. A solution in water or isotonic sodium chloride containing 5 Gm. of invert sugar in each 100 cc.

Solution Invert Sugar 10% in Water (or Saline): Abbo-Liter bottles. A solution in water or isotonic sodium chloride containing 10 Gm. of invert sugar in each 100 cc.

BAXTER LABORATORIES, INC.

Solution Travent 5% in Water (or Saline): 150 cc. and 1 liter bottles. A solution in water or isotonic sodium chloride containing 5 Gm. of invert sugar in each 100 cc.

Solution Travent 10% in Water (or Saline): 150 and 500 cc. and 1 liter bottles. A solution in water or isotonic sodium chloride containing 10 Gm. of invert sugar in each 100 cc.

U. S. trademark 534,117

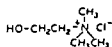
LIPOTROPIC AGENTS

Five substances possessing lipotropic properties are known to occur in nature, namely choline, betaine, methionine, inositol and β -propiethetin. The last has been found in seaweed, but its presence in materials commonly used for food has not been established. Choline is the best known and apparently most active lipotrope. It also has been used clinically more widely than the others, although comparative studies of lipotropic efficacy are lacking. The naturally occurring "lipotropic" substances also perform other functions in the body that are not associated with their lipotropic activity. Some of them may be used first for other requirements (for example, methionine for growth) before the labile methyl groups become available for lipotropic action. Folic acid and vitamin B_{12} (cyanocobalamin) also have some lipotropic effect.

Because the lipotropic effect of these substances was noted first in the liver, they have been employed extensively on this basis in the treatment of liver disease associated with fatty infiltration. In more recent years, they also have been employed in the treatment of atherosclerosis, arteriosclerosis, heart disease and various disorders of lipid metabolism.

While there is definite evidence that these lipotropic substances prevent fatty infiltration in the liver of animals receiving a choline-free diet and that they cause the disappearance of fat from the livers of animals given a hypolipotropic diet, the evidence for their clinical usefulness for such purposes at present is equivocal.

CHOLINE CHLORIDE.—(2-Hydroxyethyl)trimethylammonium chloride—The structural formula of choline chloride may be represented as follows:



Physical Properties.—Choline chloride forms white, deliquescent crystals with an amine-like odor. It is very soluble in water, freely

soluble in alcohol and practically insoluble in benzene, chloroform and ether. The pH of a 10 per cent solution is about 4.65.

Actions and Uses.—Choline chloride is considered useful as an adjunct in the treatment of fatty infiltration and early cirrhosis of the liver for those patients who cannot take an adequate diet.

Dosage.—1.5 to 3 Gm. is administered daily by the oral route, but precise dosage for this and other choline salts is not established.

ABBOTT LABORATORIES

Solution Choline Chloride: 473 cc and 3.78 liter bottles. An oral solution containing 0.135 Gm of choline chloride in each cubic centimeter. Preserved with 0.1 per cent benzoic acid and 0.04 per cent methylparaben.

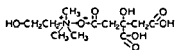
CHEMO PURO MANUFACTURING CORPORATION

Powder Choline Chloride: Bulk; for manufacturing use.

TABLEROCK LABORATORIES

Elixir Choline Chloride: 473 cc, and 3.78 liter bottles. An elixir containing 0.2 Gm of choline chloride in each cubic centimeter. Preserved with 15 per cent propylene glycol and 0.05 per cent butylparaben.

CHOLINE DIHYDROGEN CITRATE-N.F.—Chothyn Dihydrogen Citrate (FLINT, EATON)—2-Hydroxyethyltrimethylammonium citrate.—“Choline Dihydrogen Citrate, dried in a vacuum desiccator over phosphorus pentoxide for 4 hours, yields not less than 98 per cent of $C_{11}H_{21}NO_8$ on an anhydrous basis.” *N.F.* The structural formula of choline dihydrogen citrate may be represented as follows.



Physical Properties.—Choline dihydrogen citrate is a white hygroscopic, crystalline, granular substance, with an acid taste. It melts between 105 and 107.5°. It is freely soluble in water, very slightly soluble in alcohol and practically insoluble in benzene, chloroform and ether. The pH of a 25 per cent solution is about 4.25.

Actions and Uses.—Choline dihydrogen citrate shares the actions and uses of other choline salts. See the monograph on choline chloride.

Dosage.—2 to 3 Gm of choline dihydrogen citrate (8 to 12 cc. of the 25 per cent syrup) in divided doses. Choline always is administered orally.

ABBOTT LABORATORIES

Tablets Choline Dihydrogen Citrate: 0.65 Gm.

CHEMO PURO MANUFACTURING CORPORATION

Powder Choline Dihydrogen Citrate: 113.4 Gm. bottles.

FLINT, EATON & COMPANY

Capsules Chothyn Dihydrogen Citrate: 0.5 Gm.

Syrup Chothyn Dihydrogen Citrate: 475 cc. bottles. A flavored syrup containing 0.25 Gm. of choline dihydrogen citrate in each cubic centimeter.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Choline Dihydrogen Citrate: 0.65 Gm.

U. S. VITAMIN CORPORATION

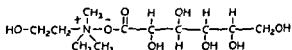
Capsules Choline Dihydrogen Citrate: 0.5 Gm.

WALKER LABORATORIES, INC.

Capsules Choline Dihydrogen Citrate: 0.25 Gm.

Tablets Choline Dihydrogen Citrate: 0.5 Gm.

CHOLINE GLUCONATE.—2-(Hydroxyethyl)-trimethylammonium *D*-gluconate.—The structural formula of choline gluconate may be represented as follows:



Physical Properties.—Choline gluconate is a straw colored, highly viscous mass possessing an amine-like odor and a bitter taste. It is soluble in water, sparingly soluble in alcohol, very slightly soluble in ether and practically insoluble in benzene and chloroform. The pH of a 50 per cent solution is between 5.0 and 6.0.

Actions and Uses.—Choline gluconate has the same actions and uses as other salts of choline. See the monograph on choline chloride.

Dosage.—Adults: orally, 12 to 15 Gm. daily in three divided doses. 2.46 Gm. of choline gluconate is required to provide the equivalent of 1 Gm. of choline base.

CHEMO PURO MANUFACTURING CORPORATION

Solution Choline Gluconate: Bulk; for manufacturing use. A solution containing 0.58 to 0.62 Gm. of choline gluconate in each cubic centimeter.

PARENTERAL FLUIDS

LACTATED POTASSIC SALINE.—LACTATED POTASSIC
row's Solution — "Lactated
solution of potassium chloride,
1 water for injection. It con-

tains, in each 100 ml, not less than 240 mg and not more than 280 mg. of potassium chloride (KCl), not less than 380 mg and not more than 420 mg. of sodium chloride (NaCl), and not less than 550 mg and not more than 630 mg. of sodium lactate ($C_3H_5NaO_3$). It contains no bacteriostatic agents" U.S.P.

Physical Properties—Lactated potassic saline in solution is a clear, colorless liquid with a pH between 6.5 and 6.7.

Actions and Uses.—Lactated potassic saline solution is used parenterally in the treatment of dehydration and acidosis associated with potassium deficiency (particularly that resulting from severe diarrhea) The solution should be employed only when the kidneys are functioning and after initial treatment of shock to ensure adequate circulation Because of its potassium content and the necessity for caution in administration, lactated potassic saline solution should not be employed promiscuously for restoration of fluids and electrolytes ordinarily replenished with other types of parenteral solutions Cardiac changes from potassium overdosage may be the only signs of toxicity. Blood potassium determinations and electrocardiographic examinations should be made frequently as precautions against these toxic effects The blood potassium should be maintained below 20 mg. per 100 cc.

Dosage—Lactated potassic saline solution is administered by hypodermoclysis when possible, by venoclysis only when necessary The total daily dose seldom should exceed 80 cc of the solution (0.216 Gm of potassium chloride) per kilogram of body weight. The rate of administration should be such as to spread the total daily dose over a period of 8 to 12 hours, and administration

patients, or with other parenteral fluids in milder cases, is essential.

For accidental potassium poisoning, 10 per cent of calcium gluconate sufficient to counteract the inhibitory cardiac effect of potassium should be administered slowly by intravenous injection

DON BAXTER, INC.

Solution Potassic Saline (Darrow): 150 and 500 cc Vacoliter bottles. A solution containing 0.27 Gm. of potassium chloride, 0.3 Gm of sodium chloride and 0.6 Gm. of sodium lactate in each 100 cc.

Oxytocics

Ergot Preparations.—Ergot, the dried sclerotium of *Claviceps purpurea* developed on rye, contains a number of specific alkaloids to which it owes its therapeutic effects. In addition, a great variety of chemical substances have been isolated from the crude drug. These include carbohydrates, lipoids, dyes, amino acids and a number of biogenous amines. Among the members of the last group are histamine, tyramine and acetylcholine, substances that are pharmacologically active but play a negligible role in the therapeutic effect of the drug.

The alkaloids thus far isolated consist of several pairs of optical isomers, one member of each pair being pharmacologically potent and the other member almost inert. The members of each pair may be interconverted by chemical procedures, and it has been suggested that the inert alkaloids may be formed to some extent from the active ones in the process of extraction.

The isomeric pairs of alkaloids may be listed as follows:

Potent	Relatively Inactive	Formula
1. Ergotoxine	Ergotinine	$C_{35}H_{39}O_6N_5$
	Ψ Ergotinine	
2. Ergotamine	Ergotaminine	$C_{33}H_{35}O_5N_5$
3. Ergosine	Ergosinine	$C_{30}H_{37}O_5N_5$
4. Ergocristine	Ergocristinine	$C_{35}H_{39}O_5N_5$
5. Ergonovine	Ergometrinine	$C_{19}H_{23}O_2N_2$

Various molecular complexes consisting of a potent and an inert alkaloid also have been isolated. These may show a pharmacologic activity different from the average of the activities of their components. In this group may be mentioned sensibamine (ergotamine plus ergotaminine) and ergoclivine (ergosine plus ergosinine).

Common to all of the above alkaloids is a hydrolysis product, lysergic acid ($C_{16}H_{16}O_2N_2$), which contains an indole group. Isomerism in the lysergic acid part of the molecule is believed to account for differences between members of the same pair. The various pairs of alkaloids differ in the other products of hydrolysis, which are unique in the field of alkaloidal chemistry in that certain of them are amino acids. These groups undoubtedly determine the variations in pharmacologic action shown by the active alkaloids of different pairs, e.g., ergotoxine and ergonovine.

Pharmacology.—Ergotoxine, ergotamine, ergosine and, presumably, ergocristine show essentially the same type of pharmacologic action although certain individual variations have been observed.

They cause a moderate and prolonged increase in tone and rhythmic contractions of the uterus by direct stimulation of smooth muscle. The blood pressure is increased in the same way, by

arteriolar constriction. The effect of ~~the~~ ~~constriction~~ ~~on~~ ~~the~~ ~~blood~~ ~~flow~~ ~~is~~ ~~that~~ ~~it~~ ~~may~~ ~~be~~ ~~lessened~~ or ~~increased~~ depending on the nature of the stimulus.

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(LILLY) —
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 $H_{23}N_3O_2$ —
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t alkaloids Dur-
to this alkaloid,
and treatment of
maleate in uterine
its high oxytocic
use prior to de-

Administered orally, intravenous administration is preferred in the neonate. In the placental transfer is rapid. In the neonate, oral or intravenous administration is necessary to repeat the dose. A dose of 0.2 mg should be given.

plate is administered
repeated two to three
perine contraction until

gastro-intestinal juices. They are effective, however, when applied to basal mucous membranes, or by injection subcutaneously or intramuscularly. Intravenous injections are hazardous and should not be undertaken except with extremely dilute solutions and under constant and intelligent observation.

The oxytocic properties of posterior pituitary have led to its use for the prevention and the treatment of postpartum and post-abort uterine atony. It is most effective in the latter case. It has been used in the induction of labor and in cases of uterine inertia during labor. It should never be used under these circumstances except in properly selected cases by capable personnel.

Systemic effects to posterior pituitary are not uncommon. "Obstetrical shock" may follow within a few seconds after intravenous injections and 30 to 60 minutes after subcutaneous injections. The patient complains of anxiety, dyspnea, occasionally precordial pain or she may be symptomless. Circulatory collapse or shock develops. The skin may assume a dusky purple or bright red color. Edema may develop. The patient may succumb. These reactions are considered to be allergic in nature.

Uses.—Oxytocics are used widely in the management of the third stage of labor to facilitate the delivery of the placenta, to decrease blood loss and to minimize the likelihood of puerperal complications. The following drug technics are in wide use:

Ergonovine (0.2 mg.) is administered intravenously as the anterior shoulder of the baby stems under the pubic arch. The baby is delivered slowly to allow the drug to exhibit its action. The separated placenta can be expressed almost immediately following the birth of the baby.

Oxytocin (10 units) is administered intramuscularly following the birth of the baby, followed by ergonovine (0.2 mg.) intramuscularly immediately after the delivery of the placenta.

Then no other oxytocic drug is administered until the placenta has been delivered. Ergonovine (0.2 mg.) is administered intramuscularly or intravenously. Posterior pituitary extract (1 cc.) or oxytocin (10 units) is administered intramuscularly. Ergonovine (0.2 to 0.4 mg.) is administered orally and repeated two or three times a day for the first 3 days.

	ERGONOVINE	ERGOTAMINE	POSTERIOR PITUITARY
Time for Effect			
Oral	6-15 min	Ineffective	Ineffective
Intramuscular	3-7 min	15-45 min	3-7 min
Intravenous	15-60 sec	5-45 min	15-60 sec.
Duration of Effect	3-8 hrs	3-8 hrs.	30-60 min
Average Dose	0.2 mg	0.5 mg	1-10 I U.
Mode of Action	Direct on muscles and sympathetic nerves	Muscle	Muscle
Type of Contraction	Tonic Clonic	Tonic Clonic	Clonic
Method of Assay	Weight	Weight	Biologic
Side Effects	Rare	More common	More common

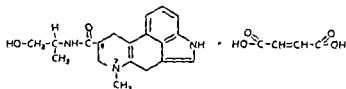
Ergotamine tartrate is of use in migraine headaches. It is not

always a prophylactic, and repeated administration will not always prevent attacks of migraine. Caution is advisable in its use because of the toxicity of overdosage or continued use.

Ergotamine is a very ineffective oxytocic drug even though it may induce uterine contractions and tone similar to ergonovine. It has little place in modern obstetric practice. Orally, ergotamine in contrast with ergonovine is absorbed so irregularly as to be unreliable for oxytocic effect by this route.

Ergotamine is contraindicated in peripheral vascular disease, severe arteriosclerosis and any other condition in which vasoconstriction would be harmful. Side effects are especially common after oral administration. They include nausea, vomiting, abdominal cramps, headache, weakness of the legs and muscle pains of the extremities. Allergic phenomena occur but are rare.

ERGONOVINE MALEATE-U.S.P.—*Ergotrate Maleate (Lilly).*—Ergometrine Maleate—"Ergonovine Maleate, dried over sulfuric acid for 4 hours, contains not less than 98 per cent of $C_{19}H_{23}N_3O_2 \cdot C_4H_4O_4$." U.S.P. The structural formula of ergonovine maleate may be represented as follows:



Physical Properties.—Ergonovine maleate occurs as a white, or faintly yellow, odorless, microcrystalline powder. It is affected by light. One gram dissolves in about 36 cc. of water, and in about 120 cc. of alcohol. It is insoluble in ether and in chloroform.

Actions and Uses.—Ergonovine maleate is a salt of one of the ergot alkaloids possessing oxytocic activity. It is effective on the uterus in smaller amounts than other potent ergot alkaloids. During the puerperium the uterus is especially sensitive to this alkaloid, and, therefore, it is useful for the prevention and treatment of postpartum hemorrhage. The use of ergonovine maleate in uterine infection is subject to question and, because of its high oxytocic potency, it is also not recommended for routine use prior to delivery of the placenta.

Dosage.—Ergonovine maleate may be administered orally, intramuscularly or intravenously. Intravenous injection is preferred in emergencies because of the rapidity of its action. In the placental stage of labor, 0.2 mg. is injected intramuscularly or intravenously after the placenta has been delivered. If it is necessary to repeat the drug because of continued bleeding, a dose of 0.2 mg. should be given intravenously.

In the postpartum period, ergonovine maleate is administered orally in doses of 0.2 to 0.4 mg. The dose is repeated two to three times daily as required to produce firm uterine contraction until

the danger of postpartum hemorrhage is past, usually after the first 3 days. In cases of delayed postpartum hemorrhage, a dose of 0.2 mg. should be given intravenously, followed by oral administration as outlined. For parenteral injection, 0.2 to 0.4 mg. is recommended as a single dose, repeated as necessary until administration by the oral route becomes feasible.

In migraine, doses of 0.2 to 0.4 mg., usually administered orally, may be given every hour until headache is relieved or a total of 2 mg. has been given.

As with other potent ergot alkaloids, prolonged therapy should be avoided; in hypersensitive individuals, care should be taken to prevent the development of ergotism.

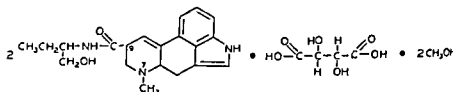
ELI LILLY & COMPANY

Solution Ergotrate Maleate: 1 cc. ampuls. A solution containing 0.2 mg. of ergonovine maleate in each cubic centimeter.

Tablets Ergotrate Maleate: 0.2 mg.

U. S. patents 2,156,242 and 2,220,801. U. S. trademark 323,111.

METHYLERGONOVINE TARTRATE.—*Methergine Tartrate* (Sandoz).—*N*-[α -(Hydroxymethyl)propyl]-*d*-lysergamide tartrate containing two molecules of methanol of crystallization.—*d*-Lysergic acid-*d*,*d*-hydroxybutylamide-2 tartrate containing two molecules of methanol of crystallization.—The structural formula of methylergonovine tartrate may be represented as follows:



Physical Properties.—Methylergonovine tartrate is a white to pinkish tan, odorless, bitter, microcrystalline powder. It is very soluble in water, freely soluble in alcohol and very slightly soluble in chloroform and in ether. Methylergonovine tartrate must be protected from light and heat. The pH of a 0.02 per cent solution is 5.0 to 5.8.

Actions and Uses.—Methylergonovine tartrate, a partially synthesized derivative of lysergic acid, closely related to ergonovine, is similar in action to the parent compound and other oxytocic alkaloids of ergot. See the general statement on oxytocics and the monograph on ergonovine maleate.

Methylergonovine tartrate induces uterine contractions in the immediate period following placental expulsion and in the puerperium by either parenteral or oral administration (within 30 to 60 seconds after intravenous injection, 2 to 5 minutes after intramuscular injection and 3 to 5 minutes after oral administration). Clinical observations indicate that the intensity and duration of

its oxytocic effect is somewhat greater than that of ergonovine maleate but less prolonged than that of ergotamine tartrate.

Methylergonovine tartrate is indicated for administration at the end of the third stage of labor or cesarean section to prevent or combat postpartum uterine atony and hemorrhage. It appears to have less tendency to produce pressor effects than does ergonovine and, therefore, may be suitable for use in the presence of pre-eclampsia or eclampsia. The drug also may be used to treat subinvolution and to combat secondary puerperal hemorrhage in conjunction with the removal of intrauterine clots. Its use in the presence of uterine infection is open to question.

Methylergonovine tartrate is contraindicated during pregnancy and should not be employed prior to delivery of the placenta unless the patient is under full obstetric supervision; then it may be given in the second stage of labor following delivery of the anterior shoulder. Laboratory experience, as well as clinical data on hand at the present, does not show this compound to have any toxic effects that are ordinarily encountered in connection with the use of the ergot alkaloids. Nonetheless the possibility of an unexpected toxic reaction should be borne in mind and physicians should be on the outlook for any untoward effects.

Dosage.—Methylergonovine tartrate is administered orally, intramuscularly or intravenously. Injection should be used immediately following delivery of the anterior shoulder or the placenta. A single dose of 0.2 mg. is injected intramuscularly or intravenously at the end of labor. If atony and hemorrhage persist postpartum, further injections of the same dose may be given at intervals of 2 to 4 hours. A dose of 0.2 mg. may be given orally three or four times daily in treating subinvolution or during postpartum convalescence in place of the parenteral route.

SANDOZ PHARMACEUTICALS, DIVISION OF SANDOZ CHEMICAL WORKS, INC.

Solution Methergine Tartrate: 1 cc ampuls. A solution containing 0.2 mg. of methylergonovine tartrate in each cubic centimeter.

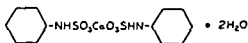
Tablets Methergine Tartrate, 0.2 mg.

U. S. patent 2,265,207 U. S. trademark 400,893.

Pharmaceutic and Therapeutic Aids

This chapter comprises pharmaceutic preparations and substances that do not contain or constitute specific therapeutic agents but are useful as aids in the formulation of topical medication or in the management and treatment of patients. It includes vehicles, such as ointment bases, suitable for compounding topical preparations of drugs and miscellaneous articles such as substitute sweetening agents and external dusting powders.

CYCLAMATE CALCIUM.—*Sucaryl Calcium* (ABBOTT).—Calcium cyclohexylsulfamate dihydrate.—The structural formula for cyclamate calcium may be represented as follows:



Physical Properties.—Cyclamate calcium is a white, crystalline, practically odorless powder with a very sweet taste. It is freely soluble in water and practically insoluble in alcohol, benzene, chloroform and ether. The pH of a 10 per cent solution is between 5.5 and 7.5.

Actions and Uses.—Cyclamate calcium is a synthetic sweetening agent for use in the diet of diabetics and other patients who must restrict their intake of carbohydrates. It may be used by patients on low sodium diets. Cyclamate calcium is essentially nontoxic, but an excessive intake may produce a laxative effect. This should be controlled by regulation of the amount used in the diet.

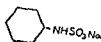
Dosage.—Cyclamate calcium is used in the form of a 15 per cent solution for the preparation of foods or to sweeten beverages. 125 cc (one-fourth teaspoonful) of a 15 per cent solution is equivalent in sweetening power to about 2 teaspoonfuls of sugar (sucrose). A bitter taste becomes noticeable when the quantity in foods approaches 0.5 per cent.

ABBOTT LABORATORIES

Solution Sucaryl Calcium: 118.3 cc bottles. A solution containing 0.15 Gm of cyclamate calcium in each cubic centimeter. Preserved with 0.1 per cent benzoic acid and 0.05 per cent methylparaben.

U. S. patent 2,275,125. U. S. trademark 536,591.

CYCLAMATE SODIUM.—Sucaryl Sodium (ABBOTT) —Sodium cyclohexylsulfamate.—The structural formula of sodium cyclamate may be represented as follows.



Physical Properties.—Cyclamate sodium is a white, crystalline, practically odorless powder with a very sweet taste. It is freely soluble in water and practically insoluble in alcohol, benzene, chloroform and ether. The pH of a 10 per cent solution of cyclamate sodium is between 5.5 and 7.5.

Actions and Uses.—Cyclamate sodium is a synthetic, stable, non-nutritive sweetening agent used as a substitute for sugar by diabetics and others who must restrict the intake of carbohydrate, and as a sweetening agent in oral forms of drugs. It is suitable to replace sugar in the diet when indicated because it is stable in hot solutions, and is free of bitter aftertaste in concentrations below 0.8 per cent. It is about 30 times as sweet as sugar. The sodium content of this preparation is a factor that must be considered in its use in patients with severe kidney damage or other conditions in which dietary sources of sodium are restricted. Cyclamate sodium is essentially nontoxic, but an excessive intake may produce a laxative effect. This should be controlled by regulation of the amount used in the diet. It is excreted somewhat slowly, about 40 per cent unchanged in the urine and 60 per cent unchanged in the feces.

Dosage.—0.125 Gm of cyclamate sodium is approximately equivalent in sweetening effect to 1 teaspoonful of sugar (sucrose). The agent is available in the form of tablets containing 0.125 Gm of cyclamate sodium with small amounts of sodium bicarbonate and tartaric acid which impart effervescence when the mixture is added to beverages. A solution containing 0.15 Gm per cubic centimeter also is marketed for its greater convenience in sweetening cold liquids and in preparing special diets.

ABBOTT LABORATORIES, INC.

Solution Sucaryl Sodium. 118.4 cc bottles. A solution containing 0.15 Gm of cyclamate sodium in each cubic centimeter. Preserved with 0.1 per cent benzoic acid and 0.05 per cent methylparaben.

Tablets Sucaryl Sodium. 0.125 Gm.
U. S. patent 2,275,125.

ABSORBABLE DUSTING POWDER—U. S. P.—Bio-Sorb (ETHCOV) —Starch-derivative Dusting Powder.—“Absorbable Dusting Powder is an absorbable powder prepared by processing cornstarch. It contains not more than 2 per cent of magnesium oxide.” U. S. P.

Physical Properties.—Absorbable dusting powder is an odorless, white powder. The pH of a 10 per cent suspension of absorbable dusting powder in water is between 10.4 and 10.8.

Actions and Uses.—Absorbable dusting powder is a light dusting

powder suitable for lubrication of the hands in donning rubber gloves and for other uses to which talcum powder ordinarily is applied in general hospital routines. As a substitute for ordinary powdered talc, it has the advantage of biologic absorbability. It is nonirritating and nontoxic. Therefore, its use avoids the hazards of talcum powder.

Absorbable dusting powder should be sterilized by autoclaving. Slight clumping which occurs after repeated autoclaving may be broken up readily with moderate pressure. Dry wall heat sterilization is not recommended for bacteriologic reasons and should be avoided also because of the possible flammability of the powder. However, even in contact with red hot cautery, the powder will flash only to about the same degree as cotton, so that flammability is not a hazard to its use in surgery.

Dosage.—An amount just sufficient to lubricate the skin or article for which a dusting powder is indicated should be applied in the same manner as ordinary talc.

ETHICON SUTURE LABORATORIES

Powder Bio-Sorb: 1.5 Gm. packets and 2.27 Kg. cans.

U. S. trademark 538,336.

ABSORBABLE GELATIN FILM.—Gelfilm (UPJOHN).—A sterile, nonantigenic, absorbable, water-insoluble, gelatin film. Absorbable gelatin film is obtained by drying on plates at constant temperature and humidity a specially prepared gelatin-formaldehyde solution. Subsequently it is sterilized by dry heat at 146 to 149° for 12 hours.

Physical Properties.—Absorbable gelatin film is a light yellow, transparent, brittle sheet 0.076 to 0.228 mm. thick, with a very slight, bouillonlike odor and taste. It is practically insoluble in acetic acid and water. It assumes a rubbery consistency after being in water for a few minutes.

Actions and Uses.—Absorbable gelatin film is used as an aid in the surgical closure of the dura mater and the meninges.

In the dry state it is brittle and stiff, but when moistened, it assumes a rubbery consistency and can be fitted to rounded, irregular surfaces. Its rate of absorption after implantation ranges from 1 to 6 months, depending upon the size of the film employed and the tissue in which it is implanted. Dural implants are absorbed less rapidly than muscle implants. When it is employed as a dural substitute, at least 70 days are required for absorption. This allows sufficient time for healing of the arachnoid layer and formation of new tissue. It also helps to prevent the formation of adhesions between the dura and the underlying tissue. It is nonantigenic and does not cause any other undesirable sequelae.

Dosage.—Absorbable gelatin film, which is approximately 0.075 mm. thick, is applied in the form of sheets. Prior to use, the film

is soaked in isotonic sodium chloride solution and then cut to the desired shape. For covering dural defects, it is applied to the surface of the brain; the edges are tucked beneath the dura, and the wound is closed in the usual manner. The moist film may be sutured loosely to the dura, but this must be done carefully to avoid tearing the material. For covering pleural defects, a similar technic is followed, except that it is preferable to anchor the film in place by means of small interrupted silk sutures.

Absorbable gelatin film may be stored indefinitely. To avoid contamination, sterile packages should not be opened until the contents are ready to be applied. When necessary, the film can be resterilized at 140° for 4 hours.

THE UPJOHN COMPANY

Gelfilm. Box of six absorbable gelatin films in individual sterile envelopes, single films are approximately 100 mm by 125 mm by 0.16 mm.

U. S. trademark 361,532

VIBESATE.—Aeroplast (AEROPLAST)—A mixture containing 93 per cent polvinat and 31 per cent malcosinol in a mixture of organic solvents and a propellant.

Actions and Uses.—Vibesate is a modified polyvinyl plastic that forms a rapidly drying, transparent, pliable and occlusive film when applied topically as a liquid spray containing a suitable volatile solvent and gaseous propellant. This film is useful as a surgical dressing, somewhat resembling that of flexible collodion. Vibesate film is semipermeable to water vapor, permitting the escape of moisture when applied to the skin. It retards the escape of fluids and electrolytes from injured areas, but it does not prevent such loss from the tissues. The transparency of the plastic film permits detection of evidence of infection in superficial wounds, and it can be peeled off readily when drainage and local anti-infective therapy become necessary.

Vibesate is useful as an occlusive surgical dressing for burns as well as for operative wounds and other surface lesions, particularly when the use of gauze or other fabricated dressings is undesirable or inconvenient. Like other local applications for burns, the film may relieve pain because of the exclusion of air. It is better adapted for dressing burns that are to be treated by the exposure method than for those treated by the older compression gauze technic. The plastic film also may replace gauze or other fabrics as a definitive surgical dressing for various closed operative incisions that do not require protective padding or the prolonged use of drains. In the open reduction of fractures it permits the application of skintight plaster casts. The film also is suitable for covering certain skin eruptions, including macerated excoriations, decubitus and traumatic ulcers and abrasions. The film usually remains intact for the period of normal healing unless the area involved is subject to considerable motion or stress; removal and

reapplication may be required to maintain occlusion or to permit proper care of contaminated wounds. There is, of course, especial danger if anaerobic organisms proliferate.

Vibesate is considered to be a relatively inert plastic and has not been reported to cause toxic, sensitivity or allergic reactions, or to interfere with healing. The volatile ethyl acetate-acetone solvent employed as a vehicle has not produced significant irritation, but transitory smarting or stinging occurs during application to sensitive surfaces. For this reason contact with the eyes or other delicate mucous membranes should be avoided. The gaseous propellant employed, a fluoro-chloro hydrocarbon, ordinarily does not come in close contact with the tissues; however, the volatile solvent and propellant are hazardous from the standpoint of accidental inhalation and flammability. Care should be taken during application to avoid inhalation of the vapors or their use near an open flame. The container should not be punctured close to an open flame or thrown into a fire.

Dosage.—Vibesate is applied topically by spraying the area of the wound or lesion to be dressed. The affected area first should be cleansed thoroughly and allowed to dry. The spray usually should be applied back and forth, parallel to the injured surface at a distance of not less than 15 cm (6 in.), preferably at about 30 cm. The spraying should include a suitable border of normal skin to afford proper anchorage. The film is allowed to dry for at least 30 seconds after each application and the spray repeated two or three times as may be required to obtain a tough, flexible film with a final thickness of 0.05 to 0.08 mm. To ensure ease of removal the film thickness should not be less than the minimum. The film may be applied directly over sutured wounds, and it may be peeled off when thoroughly dry and reapplied whenever indicated.

AEROPLAST CORPORATION

Aeroplast Spray: 170 Gm pressure cans. A spray containing 9.3 per cent polvinate and 3.1 per cent malrosinol in a mixture of organic solvents and a propellant.

U. S. trademark 582,513.

OINTMENT BASES

Ointment bases should be nontoxic, have a low index of sensitivity, a pH of 5.5 to 7.0 and should be of uniform consistency and stable with respect to the medicaments that may be incorporated. The compatibility of medicaments that are to be added should be determined. Formulas that are merely slight modifications of *U.S.P.* or *N.F.* preparations should be labeled to bear the official name, that is, "Modified———*U.S.P.* [or *N.F.*]."

The following terminology and classification for ointment bases have been adopted by an Advisory Committee on Dermatologic Vehicles.

- I. Oleaginous Ointment Base (Bases consisting of hydrophobic hydrocarbon or nonhydrocarbon oils and greases)
 1. Anhydrous Examples lard
 2. Will not take up water petrolatum
 3. Insoluble in water vegetable
 4. Not washable*
- II. Absorbent Ointment Base (Bases consisting of oleaginous materials mixed with emulsifying agents but no water)
 1. Anhydrous Examples anhydrous lanolin
 2. Will take up water hydrophilic
 3. Insoluble in water petrolatum-U.S.P.
 4. Usually are not washable*
- III. Emulsion Ointment Base
 - A. Emulsion Ointment Base W/O (Emulsions of water in oils.)
 1. Hydrous Examples cold cream
 2. Will take up water hydrous lanolin
 3. Insoluble in water
 4. Not washable*
 5. Water-in-oil emulsions
 - B. Emulsion Ointment Base O/W (Emulsions of oils in water)
 1. Hydrous Examples hydrophilic
 2. Will take up water ointment-U.S.P.
 3. Insoluble in water "vanishing creams"
 4. Washable*
 5. Oil-in-water emulsions
- IV. Water-Soluble Ointment Base
 1. Anhydrous Example. polyethylene glycols
 2. Will take up water
 3. Soluble in water
 4. Washable*
 5. Greaseless

POLYETHYLENE GLYCOL 300-N.F.—(CARBIDE & CARBON)—"Polyethylene Glycol 300 is a condensation polymer of ethylene oxide and water, represented by the formula $\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{OH}$ where n varies from 5 to 5.75. It has a molecular weight of not less than 285 and not more than 315" N.F.

POLYETHYLENE GLYCOL 400-U.S.P.—Carbowax 400 (CARBIDE & CARBON)—"Polyethylene Glycol 400 is a condensation polymer of ethylene oxide and water, represented by the formula $\text{H}(\text{OCH}_2\text{CH}_2)_n\text{OH}$, in which n varies from 8 to 10" U.S.P.

U. S. trademark 380,450

POLYETHYLENE GLYCOL 1000.—Carbowax 1000 (CARBIDE & CARBON)—A polyethylene glycol having the general formula $\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{OH}$ with an average molecular weight of about 1,000. The material is a waxy, white, semisolid that

* Water washability is hard to define. One formula for an absorbent ointment base is relatively washable, but leaves an oily residue on the skin. This does not appear to be true of either emulsion ointment base O/W or water-soluble ointment base.

melts between 37 and 40°. It is soluble to the extent of 70 per cent by weight in water at 20° and is useful in the compounding of water-soluble bases and pharmaceuticals for topical application.

U. S. trademark 380,450.

POLYETHYLENE GLYCOL 1500.—Carbowax 1500 (CARBIDE & CARBON).—“Polyethylene Glycol 1500 is a condensation polymer of ethylene oxide and water represented by the formula $\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{OH}$ where n varies from 28 to 36. It has a molecular weight of not less than 1300 and not more than 1600.” *N.F.*

low-melting petrolatum. It is insoluble in petroleum ether but completely soluble in water. It melts between 38 and 41°, and the pH of a 5 per cent aqueous solution is about 5.5.

U. S. trademark 380,450.

POLYETHYLENE GLYCOL 1540-N.F.—Carbowax 1540 (CARBIDE & CARBON).—“Polyethylene Glycol 1540 is a condensation polymer of ethylene oxide and water represented by the formula $\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{OH}$ where n varies from 28 to 36. It has a molecular weight of not less than 1300 and not more than 1600.” *N.F.*

U. S. trademark 380,450.

POLYETHYLENE GLYCOL 4000-U.S.P.—Carbowax 4000 (CARBIDE & CARBON).—“Polyethylene Glycol 4000 is a condensation polymer of ethylene oxide and water represented by the formula $\text{H}(\text{OCH}_2\text{CH}_2)_n\text{OH}$ in which n varies from 70 to 85.” *U.S.P.* It melts between 53 and 56°.

U. S. trademark 380,450.

Radioactive Isotopes

Although at present only one radioactive isotope has been evaluated by the Council for inclusion in *New and Nonofficial Remedies*, the increasing successful use of these drugs diagnostically and therapeutically seems to warrant a separate classification in anticipation of additional acceptances of similar agents

SODIUM RADIO-IODIDE (I^{131}).—SODIUM RADIO-IODIDE (I^{131}) SOLUTION—U S P—Radioactive Iodine Solution— NaI^{131} —“Sodium Radio-iodide (I^{131}) Solution is a solution containing iodine-131 suitable for either oral or intravenous administration. Iodine-131 is a radioactive isotope of iodine processed in the form of sodium iodide from the products of uranium fission in such manner that it is essentially “carrier-free” and contains only minute amounts of naturally occurring iodine-127. Sodium Radio-iodide (I^{131}) Solution contains a suitable bacteriostatic agent.

“Sodium Radio-iodide (I^{131}) contains not less than 95 per cent and not more than 105 per cent of the labeled amount of I^{131} as iodide expressed in microcuries or millicuries, at the time indicated in the labeling. Iodine-131 activity as iodate does not exceed 5 per cent of the iodide activity. Other chemical forms of radioactivity are absent.

“**Caution—**Dosage calculations must take into account radioactive decay. The half-life of Iodine-131 is 80 days. To prevent the I^{131} from being adsorbed, all containers used to handle Sodium Radio-iodide (I^{131}) Solution should be previously rinsed with a solution containing approximately 0.80 per cent of sodium hydroxide, 0.04 per cent of sodium bisulfite, and 0.25 per cent of sodium iodide followed by rinsing with purified water until the last rinsing is neutral to litmus” U S P.

Actions and Uses.—Sodium radio-iodide (I^{131}) is used in the form of solutions freshly prepared from the radioactive isotope, I^{131} . It is useful in solutions of appropriate concentration for diagnostic studies in patients with suspected thyroid disease, for treatment of selected cases of thyrotoxicosis and, in conjunction with other agents and methods, for the palliative treatment of carcinoma of the thyroid gland and metastatic lesions arising from it. It is used also to detect distant metastatic growths of thyroid carcinoma and to determine whether intact tissue or a tumor mass is of thyroidal origin. It may be used to induce hypothyroidism in euthyroid patients with angina pectoris to aid in the management of that condition.

The accumulation of radio-iodine in the thyroid gland probably

reflects, to a large extent, the formation of diiodotyrosine and thyroxine and the storage of these compounds in the thyroid follicle. At first, iodine may be present in the inorganic form (NaI), but in a short time it becomes protein-bound, apparently linked with the tyrosine radical, in the gland. Patients who have little or no functioning thyroid tissue, particularly with the clinical syndrome of myxedema, usually excrete considerably more of the diagnostic dose in the urine during the first 24 to 72 hours than do normal subjects. The uptake of radio-iodine may be depressed by prior intake of stable iodine in any form or by the use of thyroid substance or of antithyroid drugs. Among the many iodine-containing preparations and compounds that may contain dissociable iodine are the following:

1. External iodine preparations
 - a. Ointments and solutions of iodine or iodides
 - b. Tinctures of iodine or iodides
 - c. Iodoform gauze
2. Internal iodine preparations.
 - a. Strong iodine solution (compound iodine solution, Lugol's solution)
 - b. Potassium iodide and potassium iodide solution
3. Asthma, cough and vitamin preparations containing iodine compounds.
4. X-ray contrast media
 - a. Contrast media, such as iodinated contrast media
 - b. Iodinated contrast media, such as iodinated contrast media
 - c. Iodinated contrast media, such as iodinated contrast media
 - d. Myelographic media, both of the oily and aqueous type containing iodine
 - e. Cavity and sinus visualization media, such as sodium iodide and chloriodized and iodized oils
5. Antiparasitic drugs
 - a. Iodochlorhydroxyquin
 - b. Diiodohydroxyquin
6. Thyroid extract, thyroxine.
7. Iodinated antithyroid drugs, such as liothyronine sodium

Other antithyroid drugs, particularly those of the thiourea series and methimazole, also influence the uptake of radio-iodine by the thyroid gland. The effect of these drugs is to inhibit the synthesis of thyroid hormone.

presence of pregnancy.

range. None are to be used in the treatment of leucocytes that returns

side effect.

Dosage.—Sodium radio-iodide is administered orally or intravenously in aqueous solutions of appropriate concentration. It should be emphasized that there is always a difference between the dosage administered and the amount taken up by the gland and

be as much as 100 microcuries or more

The therapeutic dose to be administered usually is calculated after a diagnostic test to determine the per cent absorbed by the gland in a specified time, e.g., 24 hours. For the treatment of thyrotoxicosis, a single or fractional dose procedure may be used. With an estimated uptake of about 70 per cent, the single dose administered usually is 105 to 180 microcuries per estimated gram of thyroid tissue, so as to provide a retained dose of about 75 to 125 microcuries per gram. Accurate estimate of the amount of thyroid tissue may be difficult and should be considered carefully to avoid error in the calculation of dosage. In the majority of patients, the single dose should not exceed 8 millicuries. Any further dosage usually is not considered before 6 months has elapsed. If the fractional method of dosage is used, the initial dose is considerably less and the usual interval between doses is about 6 weeks to 2 months

may be given after an interval of not less than 60 days when additional antithyroid therapy is required

Since the treatment of thyroid carcinoma and metastases is unique for each case, no information on the dosage for these conditions is included

The decay in radioactivity of solutions, based on the half-life of the radioisotope, makes it necessary to correct the labeled content immediately or at least in accordance with the time that

of various concentrations

ABBOTT LABORATORIES

Diagnostic Solution Sodium Radio-Iodide (I^{131}): 10 cc. vials. A solution containing 25 microcuries of sodium radio-iodide in each cubic centimeter.

Therapeutic Solution Sodium Radio-Iodide (I^{131}): 10, 20 and 30 cc. vials. Solutions containing 5 to 15 millicuries, 15 to 40 millicuries and 40 to 100 millicuries, respectively.

Sclerosing Agents

Solutions of ethyl alcohol, dextrose, invert sugar, iodides, iron salts, mercuric chloride, phenol, quinine and urea hydrochloride, salicylates, sodium chloride, sodium citrate, sodium morrhuate and others have been employed as sclerosing agents, mainly for the obliteration of varicose veins. Some of the compounds employed for this purpose are combined with local anesthetic agents or themselves possess anesthetic properties. Solutions of dextrose or invert sugar and fatty acid preparations such as sodium morrhuate

hemorrhoids. Sclerosing therapy of varicose veins is contraindicated in the presence of incompetency of the collateral deep veins of the lower extremities and before ligation of the greater saphenous vein in the presence of incompetency of the valves of that vein. Other contraindications include active or recent phlebitis, systemic diseases such as active tuberculosis and hyperthyroidism, acute infections (including the common cold), prolonged recumbency, occasional case legs, and recurs of a sclerosing

SODIUM PSYLLIATE.—SODIUM PSYLLIATE INJECTION.—N.F.—Sylasol (SEARLE).—"Sodium Psylliate Injection is a sterile solution of the sodium salts of the 1, 2, and 3 fatty acids obtained by

Their pH is between 8.7 and 9.2.

Actions and Uses.—Sodium psylliate is used in the form of a 5 per cent solution as a sclerosing agent for the obliteration of varicose veins of the lower extremities and of selected internal hemorrhoids that are not prolapsed or thrombosed. It is not recommended for other types of hemorrhoids.

Its sclerosing action is approximately equivalent to that of other fatty acid salts and it is subject to about the same frequency of allergic reaction to repeated use.

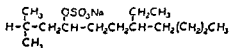
Dosage.—A 5 per cent solution of sodium psyllate is injected in amounts dependent upon the size of the varicosity to be obliterated. The dose may vary from a few minims in suitable internal hemorrhoids, to 5 or 6 cc. for large sacculated veins of the lower extremities. The large doses should be given no oftener than twice weekly and single doses in excess of 6 cc. should be avoided. It is advisable to inject a test dose of 0.5 to 1 cc. to detect possible idiosyncrasy before commencing therapy. Treatment should be discontinued when severe reactions occur or are suspected.

G. D. SEARLE & Co.

Sclerosing Solution Synasol 5% with Benzyl Alcohol 2%: 5 cc and 60 cc. vials. An aqueous solution containing 50 mg. of sodium psyllate in each cubic centimeter.

U. S. patents 2,115,491 and 2,115,492, U. S. trademark 340,714.

SODIUM TETRADECYL SULFATE.—Sodium Sotradecol (WALLACE & TIERNAN).—Sodium 7-ethyl-2-methyl-4-hendecanol sulfate.—The structural formula of sodium tetradecyl sulfate may be represented as follows:



Physical Properties.—Sodium tetradecyl sulfate is a white, waxy, odorless solid. It is soluble in alcohol, ether and water. A 5 per cent solution is clear and colorless, and has a pH between 6.5 and 9.0.

Actions and Uses.—Sodium tetradecyl sulfate is an anionic surface-active agent useful as a wetting agent to increase the surface activity of solutions of certain externally applied antiseptics to which it may be added. It also possesses sclerosing properties useful for the obliteration of varicose veins and internal hemorrhoids that are not prolapsed or thrombosed. Its rather profound sclerosing action is subject to the disadvantage that injections outside of the vein may produce sloughing and that injection into the veins, especially in the higher dosage, frequently may be associated with pain. On the rare occasions when severe reactions are remote and the reactions are mild and of short duration have been discovered.

Sodium tetradecyl sulfate is subject to the same contraindications as other sclerosing agents. See the general statement on sclerosing agents.

Dosage.—For sclerosis of varicose veins, buffered solutions of sodium tetradecyl sulfate are used; the concentrations employed are 1, 3 or 5 per cent, depending on the size of the veins (amount of hemodilution) to be obliterated. It is recommended that not

more than 1 cc. of the 1 per cent concentration be used as a test dose on the first injection to detect idiosyncrasy. The 3 per cent concentration is adequate for most sites. To avoid sloughing that may occur with the 1 per cent concentration, the dose should be 0.5 to 1 cc. and at any one sitting, 2 to 3 cc. Not more

cent solution of sodium tetradecyl sulfate is recommended, smaller amounts of the 3 per cent solution may be employed, but with a greater risk of sloughing. Higher concentrations should not be used. The initial dose of the 1 per cent solution should be 0.5 cc.; and the dose may be gradually increased to a maximum of 1.5 to 2 cc. at the fifth or sixth injection. When the 3 per cent solution is employed, the initial dose should be 0.2 cc. and the maximum 0.6 cc. Injections should be made at intervals of 5 to 7 days, four to twelve injections being required. Injection too near the anorectal line should be avoided since it may cause pain.

WALLACE & TIERNAN, INC.

Solution Sodium Sotradecol with Benzyl Alcohol 2%: 20 cc vials. A solution containing 10, 30 or 50 mg of sodium tetradecyl sulfate in each cubic centimeter.

U. S. patent 2,497,742 U. S. trademark 428,131.

Skeletal Muscle Relaxants and Their Antagonists

Formerly, it was customary to divide the skeletal muscle relaxants into two main groups, those acting on, or in the vicinity of, myoneural juncture and those affecting the basal ganglia and the reflex of excitability of nerve centers. Those that block the myoneural juncture were grouped into the drugs called the curares and the curarelike drugs. This group consisted of the naturally occurring curare alkaloids that act by raising the threshold of the myoneural junction and the synthetic drugs that act by local depolarization. An example of those that act on the reflex excitability would be mephenesin. However, it now appears that the past division into two groups may be less sound than it was originally believed. Both clinical and laboratory evidence indicate that several, possibly most, of the agents that paralyze the neuromuscular end-plate also interfere seriously with the circulation, apparently, in part at least, by block of ganglia.

This entire group of drugs has its chief usefulness in the production of relaxation during surgical anesthesia, in the production of relaxation of muscles for manipulation during orthopedics and similar manipulations, in eye and rectal surgery, for protection against trauma during electric shock, for relaxation of anesthetized muscles and for relaxation of muscles following trauma from operative procedures or from other pathologic states such as back strain, anterior poliomyelitis and various spastic states.

When the skeletal muscle relaxing drugs were first used, it was expected that they would permit a lowering of the operative mortality rate by permitting the surgeon to do effective work under lighter and presumably less hazardous anesthesia than usual. Undoubtedly, the total dose of anesthetic can be diminished for certain operations by the use of these agents; but the increasing evidence indicates that their undoubted advantages have been attained at a price of occasional untoward effects and sometimes of serious difficulty.

It is well known that the skeletal muscle relaxants may cause respiratory failure. The margin of safety between the dose necessary to produce good relaxation of voluntary muscles and that which paralyzes respiration unfortunately is small; but if failure of respiration is detected promptly and treated energetically by artificial respiration and oxygen, recovery is rapid and usually is not accompanied by any untoward after effects. Clearly, facilities for satisfactory artificial respiration always must be at hand when

the muscle relaxants are to be used. Edrophonium chloride may be used as a supplement to these measures, especially after prolonged curarization, but only if some sign of voluntary respiration can be observed. Otherwise, overdosage may result.

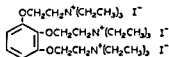
Much more serious than the respiratory problem is the circulatory collapse occasionally seen in patients given these agents, even in dosages not exceeding those usually well tolerated. This circulatory collapse is demonstrated easily in animal experiments after overdosage. This collapse does not always respond to such measures as intravenous injections of blood, blood substitutes or vasoconstrictor drugs. Antidotes, such as neostigmine and physostigmine, often are of little or no assistance and are contraindicated with succinylcholine.

Toxic manifestations suggesting involvement of the central nervous system, effects which again may be demonstrated in animals after overdosage, are seen occasionally in patients after proper doses of these drugs. These serious forms of toxicity may be difficult or impossible to handle satisfactorily.

The operative mortality rate in good hospitals now is low enough so that individual surgeons and anesthetists may not encounter a death for long periods, but certain evidence has led to the contention that operative mortality has been increased significantly when these drugs have been used.

As the muscle relaxants are of great pharmacologic power and are not devoid of danger, they should be used only when an important advantage can be gained for the patient.

(LEDERLE).
iodide] —
structural
as follows:



Physical Properties—Gallamine triethiodide is a white, fluffy, hygroscopic powder. It is freely soluble in water, soluble in alcohol, very slightly soluble in chloroform and insoluble in ether. A 2 per cent solution is clear and colorless and has a pH of about 5.8.

Actions and Uses—Gallamine triethiodide, a synthetic substituted quaternary amine compound similar in action to curare, is useful to relax skeletal muscle for the same purposes and with the same precautions as other curarelike agents. (See the general statement on curare.) Unlike curare and its derivatives, gallamine triethiodide exhibits little action on autonomic ganglia. It is useful with general anesthesia to provide more complete muscular relaxation during surgical, manipulative, endoscopic and intubation procedures. It is used also to prevent accidents during convulsive shock therapy and to reduce muscle spasm during nonoperative orthopedic procedures.

Further observations are needed to confirm its usefulness in obstetrics and for the management of convulsions and chronic spastic states secondary to disease.

Like all potent curarelike drugs, gallamine triethiodide should be used only by those thoroughly familiar with such agents, and only when facilities for intubation, artificial respiration, oxygen therapy and administration of antidotes are immediately available.

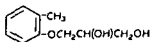
Gallamine triethiodide may produce allergic reaction in patients sensitive to iodine and care should be taken to avoid severe reactions of this type. The drug is absolutely contraindicated in patients with myasthenia gravis.

Dosage.—Gallamine triethiodide is administered by intravenous injection as an aqueous solution. The dosage should be individualized by careful observation of the patient. The theoretical initial dose is about 1 mg per kilogram of body weight. For prolonged procedures, additional doses of 0.5 to 1 mg per kilogram may be injected at intervals of 40 to 50 minutes. Like curare, its action is cumulative.

The drug is readily miscible with solutions of thiopental sodium. In conjunction with ether inhalation anesthesia, smaller doses are required than for other general anesthetics. The same antagonists that are effective against tubocurarine will interrupt the action of gallamine. Neostigmine methylsulfate 0.5 mg. to 1.5 mg. is a useful antidote and atropine sulfate may be administered simultaneously to counteract the postganglionic effect of neostigmine. A larger dose of the antidote is needed when gallamine is used in conjunction with ether because the latter impedes removal of the drug. Antidotes should be used with caution in asthmatic patients sensitive to such drugs. Such adverse antidotal effect also is counteracted with atropine.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

MEPHENESIN-N.F.—Daserol (EVRON)—Dioloxol (CARRICK)—Mepherol (BRYANT)—Mephson (TUTAG)—Myoxane (ASCHER)—Oranixon (ORGANON)—Sinan (WARREN-TEED)—Tolansin (PHYSICIANS' DRUG)—Tolserol (SQUIBB)—Tolulox (MILLER)—3-*o*-Toloxyl-1,2-propanediol—"Mephenesin contains not less than 96 per cent of $C_{10}H_{14}O_3$." *N.F.* The structural formula of mephenesin may be represented as follows:



Physical Properties.—Mephenesin is an odorless, crystalline, white powder which melts between 67 and 72°. It is freely soluble in

alcohol, chloroform and ether and sparingly soluble in benzene and water. The pH of the saturated solution is about 6.

Action and Uses.—Mephenesin may be relieved of muscular weakness. The drug may be tried in any situation in which muscular weakness is present.

The drug has been used to obtain muscular relaxation in surgical anesthesia, but its use for this purpose is decreasing because of the large doses necessary and because in concentrations greater than 1 per cent hematuria may develop. Mephenesin also has a local anesthetic effect.

Mephenesin has a sedative action and it produces a definite, but temporary, improvement in certain psychotic states. The unexpectedly severe sedative action which may result from accumulation of mephenesin with barbiturates is a drawback to its use to secure muscular relaxation during barbiturate anesthesia.

The drug may be used in anxiety tension states as an adjunct to psychotherapy to demonstrate to the patient what is meant by a state of relaxation. Its continued use for such conditions is not advised.

Untoward effects have been infrequent. After intravenous injections, weakness, nystagmus, diplopia and mild muscular incoordination have occurred. Side effects usually have been absent following oral administration, although, occasionally, lassitude has resulted, and leukopenia has been encountered rarely. The development of tolerance has been suspected.

Mephenesin is of great interest because of its action on the central nervous system.

2
5

Dosage.—For adults, 1 to 3 Gm. given orally three to five times a day. The dosage should be spread evenly throughout the waking hours. If a favorable response is not seen within 72 hours, the drug should be discontinued.

As a diagnostic aid, 30 to 150 cc. of a 2 per cent solution of mephenesin may be infused intravenously at a rate of 30 to 40 drops per minute.

AMERICAN PHARMACEUTICAL COMPANY

Tablets Mephenesin: 0.5 Gm.

B. F. ASCHER & COMPANY, INC.

Tablets Myozane: 0.5 Gm.

THE BOWMAN BROS. DRUG COMPANY

Tablets Mephenesin: 0.5 Gm.

BRYANT PHARMACEUTICAL COMPANY

Tablets Mepherol: 0.25 and 0.5 Gm.

G. W. CARRICK COMPANY

Capsules Dioloxol: 0.25 Gm.

Elixir Dioloxol: 473 cc. and 3.78 liter bottles. A solution containing 0.1 Gm. of mephenesin in each cubic centimeter.

Tablets Dioloxol: 0.25 and 0.5 Gm.

U. S. trademark 547,121.

THE EVRON COMPANY, INC.

Tablets Daserol: 0.25 and 0.5 Gm.

GOLD LEAF PHARMACAL COMPANY, INC.

Tablets Mephenesin: 0.5 Gm.

VICTOR M. HERMELIN & COMPANY, NEW PRODUCTS DIVISION OF
KEITH-VICTOR PHARMACAL COMPANY

Tablets Mephenesin: 0.25 and 0.5 Gm.

HEXAGON LABORATORIES, INC.

Powder Mephenesin: Bulk; for manufacturing use.

C. B. KENDALL COMPANY

Tablets Mephenesin: 0.25 and 0.5 Gm.

KREMERS-URBAN COMPANY

Tablets Mephenesin: 0.5 Gm.

E. S. MILLER LABORATORIES, INC.

Elixir Tolulox: 237 cc. and 3.78 liter bottles. A 5 per cent alcohol, 40 per cent propylene glycol solution containing 0.2 Gm. of mephenesin in each cubic centimeter.

Tablets Tolulox: 0.25 and 0.5 Gm.

ORGANON, INC.

Elixir Oranixon: 237 and 473 cc. and 3.78 liter bottles. A 20 per cent alcohol solution containing 0.1 Gm. of mephenesin in each cubic centimeter. Preserved with 0.037 per cent methylparaben and 0.025 per cent propylparaben.

Tablets Oranixon: 0.25 and 0.5 Gm.

U. S. trademark 532,165.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Tolensin: 0.25 and 0.5 Gm.

Actions and Uses.—Succinylcholine chloride is a myoneural blocking agent that produces a skeletal muscle relaxant effect somewhat resembling that of curare and curarelike compounds. It likewise produces muscle relaxation as an adjunct to anesthesia during surgical procedures and in conjunction with electroshock therapy. Succinylcholine chloride is a shorter-acting drug than tubocurarine chloride and, therefore, is suited particularly for endotracheal intubation, endoscopy and other short, manipulative procedures. In contrast with tubocurarine chloride, succinylcholine chloride is not antagonized by anticholinesterases; and the injection of such drugs as physostigmine, neostigmine, procaine or edrophonium prolongs its action. This suggests that the short action of the drug is caused by relatively rapid hydrolysis of the ester linkage by enzyme action, such as that of cholinesterases. Presumably, the drug is hydrolyzed rapidly into nontoxic choline and succinic acid and is not dependent on the liver or kidneys for detoxication or excretion.

Tachyphylaxis or cumulative action is not encountered ordinarily, but like other myoneural blocking agents, succinylcholine chloride in extremely high doses may produce respiratory depression, persisting after the diaphragmatic response to phrenic nerve stimulation has returned. Facilities for controlled, involuntary respiration and for the administration of oxygen to secure adequate

with severe liver disease, severe anemia and malnutrition or in those suffering from polyphosphate insecticide poisoning who may have decreased plasma-cholinesterase activity that might intensify and prolong the action of the drug. In such patients, artificial respiration and oxygen therapy may be supplemented by the administration of plasma or whole blood to restore cholinesterase activity.

Because succinylcholine chloride is hydrolyzed rapidly by alkaline solutions, it loses its potency rapidly when mixed with thiosulfate sodium. For this reason, separate injection is preferable.

Succinylcholine chloride is quite stable when stored under refrigeration. When exposed to light, its potency gradually decreases, so that solutions may be kept for a short period without significant loss of potency.

Dosage.—Succinylcholine chloride is administered in solution by the intravenous route, either as a single intermittent injection or as a continuous drip infusion.

For short procedures, the suggested adult dose is 20 mg. for a single injection; the optimum dose ranges from 10 to 30 mg. Within this range each such dose usually produces relaxation in about 1 minute. Maximum muscular relaxation may persist for about 2 minutes, followed by rapid recovery within the next few minutes. Since the maximum safe dosage of the drug has not been determined, and since the response obtained may vary in different

patients, careful observation of respiratory exchange is essential to avoid paralytic apnea

For prolonged procedures, sustained relaxation may be obtained with a continuous intravenous drip infusion at a dosage rate of 0.5 to 10 mg (average 2.5 mg) per minute for adults. The solution of the drug to be infused may be prepared by dilution of 500 mg of succinylcholine chloride in 250 or 500 cc of sterile isotonic sodium chloride solution or 5 per cent dextrose solution, thus providing a 0.1 per cent (1 mg per cubic centimeter) or a 0.2 per cent (2 mg per cubic centimeter) solution, respectively. The degree of relaxation can be altered in approximately 30 seconds by regulating the rate of the drip infusion. Careful supervision of the infusion and the control of respiration are absolutely essential to avoid hypoxia.

ABBOTT LABORATORIES

Solution Quelicin Chloride: 10 cc vials. A solution containing 20 mg of succinylcholine chloride in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

10 cc. ampuls: A solution (to be diluted for intravenous infusion) containing 50 mg of succinylcholine chloride in each cubic centimeter.

U. S. trademark 587,354

BURROUGHS WELLCOME & COMPANY, INC

Solution Anectine Chloride: 10 cc vials. A solution containing 20 mg of succinylcholine chloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

10 cc ampuls: A solution (to be diluted for intravenous infusion) containing 50 mg of succinylcholine chloride in each cubic centimeter.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Solution Succostin Chloride: 10 cc vials. A solution containing 20 mg of succinylcholine chloride in each cubic centimeter.

10 cc ampuls: A solution (to be diluted for intravenous infusion) containing 50 mg of succinylcholine chloride in each cubic centimeter. Both sizes preserved with 0.1 per cent methylparaben and 0.01 per cent propylparaben.

U. S. trademark 596,644

CURARE

Curare frequently has been a pharmacologic agent for laboratory investigation, but only recently has it come into use as a therapeutic agent. The crude drug is a plant extract prepared by various tribes of South American Indians for use as arrow poisons. The Indians classified types of curare according to the containers in which they were stored. Originally this nomenclature also distinguished chemically different curares. Thus, tube curare, pot curare

and calabash curare each contained different alkaloids. However, since the changing habits of Indians have rendered the container nomenclature invalid for chemical classification, the chemical distinctions themselves now are used.

Tube curare has been investigated thoroughly. A physiologically active alkaloid called tubocurarine chloride was isolated in crystalline form from this material in 1935. In 1943 it was found in extracts of the plant species *Chondodendron tomentosum*.

The other types of curare, calabash and pot curare, have been examined less thoroughly, but several active crystalline alkaloids have been isolated from calabash curare. The plant species *Strychnos toxifera* in the region of the Orinoco River is the natural source of this curare. It is different from those in tube curare. The alkaloids of pot curare are quaternary ammonium salts. The quaternary ammonium salt of the active principle of pot curare has not been obtained.

Other alkaloids associated with this fraction indicate similarity between the alkaloids of pot curare and tube curare.

Curare has been used as a generic term that includes all drugs acting in the vicinity of the myoneural junction. It is sounder, however, to refer to these agents as "the muscle relaxants," since some of the newer agents are not similar to the original curare. It should be emphasized that each drug has its own inherent characteristic pattern of progression of relaxation and also its own inherent pattern of comparative depression of various muscular groups, so that each has a ratio of relaxation dose to total apnea dose. The safety of each of the curares will depend to a degree upon the ratio of the relaxing dose to the apnea dose, the duration of action and the severity and type of side reaction, such as vascular depression and synaptic or ganglionic blocking action. No one drug of all the curares is superior except in certain characteristics. Early recognition that the active curare alkaloids are quaternary ammonium bases led to the observation that other quaternary compounds possess varying degrees of curariform activity and to the synthetic preparation of a great number of such compounds. The only compounds which possess curare activity but are not quaternary bases are the Erythrina alkaloids. These alkaloids occur in the seeds of many species of Erythrina; they are tertiary bases but possess true peripheral curare activity.

Curare in therapeutic dosage blocks myoneural transmission to skeletal muscle. Moderate clinical doses also may depress ganglionic transmission in the autonomic nervous system. They also progressively depress the autonomic ganglia, the degree of block varying from drug to drug. In some persons the predominant effect is on the sympathetic nerves, while in others the effect is predominantly on the parasympathetic nerves. These effects have been used clinically to interrupt reflex activity such as vagovagal or vagosympathetic reflexes. The blocking action of curare on the somatic nerves to skeletal muscles is analogous to that of atropine on the parasympathetic nerves to certain smooth muscles. The autonomic action of curare simulates that of nicotine but to a lesser degree and

without an initial stimulant phase. Thus, curare is an antispasmodic of skeletal muscle, reducing the tone or contractile power by specific peripheral effect. Some of the synthetic curaremimetic drugs do, however, show the stimulation prior to depression. This becomes evident with the use of such drugs as decamethonium where fibrillatory muscular twitching can be seen prior to the blockade.

Therapeutic doses produce the following sequence of skeletal muscle depression: heaviness of the eyelids, diplopia, except for distant vision, difficulty in swallowing and talking; progressive weakness of extremities and neck, then the trunk and spine, the intercostals and, lastly, the diaphragm. The effect of therapeutic doses depends on such factors as what drug is injected, rate of injection, concentration of drug used, depth and type of anesthesia, over-all body mass, muscular mass and physiologic state of patient. This sequence of depression nearly parallels the order of involvement in myasthenia gravis. Paralysis recedes in reverse order after the full effect is manifest, the extent and duration of action depending on the size of the dose. Recovery may require from 20 to 30 minutes following the ordinary single intravenous dose.

because these drugs, in their bases, potentiate rather than antagonize curare activity. Moreover, prompt and adequate artificial respiration is the important factor in the treatment of overdosage with curares, and the anticurares are of secondary and limited value.

Curare preparations for therapeutic use are made in partially purified form and in the form of pure or modified tubocurarine. Until more is known of their alkaloidal content, curare preparations from various sources should be bio-assayed for potency, although the crystalline chloride salt of tubocurarine may be prescribed on a weight basis. Preparations of *d*-tubocurarine are being prepared with negligible residue and very slight deviation in optical rotation, indicating a great degree of purity. Thus, the drug now can be dispensed by weight alone, the bio-assay being used as a check. The potency of curare is measured by the "head-drop" bio-assay

in curare overdosage.

The curares seem to supplement the effect of various anesthetic agents, but tests such as those for analgesic or psychomotor activity and electroencephalogram pattern have not produced evidence to substantiate this clinical impression. Some of the data on the stimulating effect on the central nervous system, gained from experiments on animals, probably is due to the anoxia secondary to partial respiratory paralysis produced by the drug.

Whenever curares are to be used, a test dose should be administered prior to the curarizing dose and allowed to reach its maximal effect. For most of the curares, the time necessary for this is approximately 5 minutes.

Use of curare drugs is hazardous in conditions of shock where peripheral pooling of blood in the venous plexus has resulted from relaxation of the muscles, thus diminishing the cardiac return and subsequently the cardiac output. In addition, many of these drugs block synaptic transmission and, therefore, cause a peripheral vascular dilatation and potentiate shock. Thus, they should be avoided, especially those that block the synaptic ganglia in states of potential shock.

Repeated dosages of curare drugs should be given with extreme caution, since they are known to have a marked effect on the heart, and at the same time, they may cause a marked effect on the respiratory system. The available data may indicate that the curare drugs are not safe for use in patients with heart disease or respiratory failure.

Curare drugs in oil must be used with caution because absorption in most products is not uniform and, therefore, the response to the drug cannot be predicted. They should be administered only after careful testing and under adequate supervision.

CHONDODENDRON TOMENTOSUM EXTRACT, PURIFIED.—**Intocostin (Squibb).**—An aqueous preparation containing therapeutically effective constituents of crude curare. It is prepared by extracting with alcohol a desiccated curare obtained from a heavy syrup of the bark and stems of the *Chondodendron tomentosum*. The curare activity is due almost wholly to the presence of an alkaloid, tubocurarine, which accounts for about half the total solids in purified chondodendron tomentosum extract, exclusive of added sodium chloride and chlorobutanol. The physiologic activity of purified chondodendron tomentosum extract is determined on rabbits. The unit is a potency equivalent to that of 0.15 mg of a pure or recrystallized tubocurarine chloride pentahydrate containing the theoretical water content of 11.46 per cent.

Intocostin is used for the same purposes as its active principle, tubocurarine. See the monograph on tubocurarine chloride.

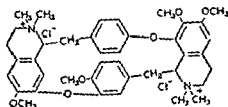
Dosage.—See the monograph on tubocurarine chloride.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Solution Intacostin: 10 cc vials. A sodium chloride solution containing the equivalent of 20 units of purified chondrodendron tomentosum extract in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

U. S. trademark 382,110

DIMETHYL TUBOCURARINE CHLORIDE—Mecostin Chloride (SQUIBB)—O-Methyl-d-tubocurarine chloride—Dimethyl ether of d-tubocurarine chloride—The structural formula of dimethyl tubocurarine chloride may be represented as follows:



Physical Properties.—Dimethyl tubocurarine chloride is a white, odorless, crystalline powder. It decomposes with evolution of gas when heated to about 236°. It is soluble in water and diluted sodium hydroxide, sparingly soluble in alcohol and diluted hydrochloric acid, very slightly soluble in chloroform and practically insoluble in benzene and ether.

Actions and Uses.—Dimethyl tubocurarine chloride has the same actions and uses as dimethyl tubocurarine iodide and tubocurarine chloride except that the efficacy of the methylated derivatives in the treatment of spastic diseases has not yet been determined. (See the monographs on dimethyl tubocurarine iodide and tubocurarine chloride.)

Dosage.—Dimethyl tubocurarine chloride has approximately the same ratio of potency as dimethyl tubocurarine iodide when compared with tubocurarine chloride, but on the basis of the difference in the molecular weights of the two salts, 0.8 mg. of dimethyl tubocurarine chloride provides a dose equivalent to 1 mg. of the iodide. Like the iodide, dimethyl tubocurarine chloride is administered only by slow intravenous injection over a period of 30 to 60 seconds. For muscle relaxation in surgery, the average initial dose for adults is 2 to 3 mg. If needed, 1 to 1.5 mg. can be added in 3 to 5 minutes. After 45 minutes, an additional dose of 1.5 to 2 mg. may be administered. With ether anesthesia the dose of dimethyl tubocurarine chloride should be about one-third that used with other anesthetic agents. For shock therapy and manipulative therapy the average dose is calculated on the basis of 0.025 mg. per pound of body weight, using 1 mg. less than this amount for the initial dose in adults. The safe upper limit of dosage is 0.037 mg. per pound of body weight. As a diagnostic agent in myasthenia gravis, the dose is one-fortieth to one-tenth of the

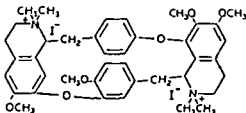
adult shock therapy dose (ie, 0.0006 to 0.0025 mg. per pound of body weight), administered intravenously. The test always should be terminated within 2 or 3 minutes by the intravenous injection of 1.5 mg. of neostigmine methylsulfate with 0.6 mg. of atropine sulfate. The same precautions and contraindications should be observed as with other purified derivatives of curare.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Solution Mecostrin Chloride: 10 cc. vials. An isotonic salt solution containing 1 mg. of dimethyl tubocurarine chloride in each cubic centimeter. Preserved with 0.9 per cent benzyl alcohol.

U. S. trademark 563,029.

DIMETHYL TUBOCURARINE IODIDE-N.F.—Metubine Iodide (LILLY).—Dimethyl ether of *d*-tubocurarine iodide.—O-Methyl-*d*-tubocurarine iodide.—The structural formula of dimethyl tubocurarine iodide may be represented as follows:



Physical Properties.—Dimethyl tubocurarine iodide is a white to pale yellow, odorless, crystalline powder. It decomposes with the evolution of gas when heated to about 257°. It is slightly soluble in water, diluted hydrochloric acid and diluted sodium hydroxide, very slightly soluble in alcohol and practically insoluble in benzene, chloroform and ether.

Actions and Uses.—Dimethyl tubocurarine iodide shares the curare action of tubocurarine chloride. The methylated derivative of the alkaloid produces respiratory paralysis less frequently. Clinically, the ratio of potency of dimethyl tubocurarine to *d*-tubocurarine is slightly less than 3:1.

Dimethyl tubocurarine iodide is useful for the same purposes as tubocurarine chloride, except that its efficacy in the control of spastic conditions has not been studied completely, but it would seem to have a greater safety factor because of the relation of its relaxation dose to the apnea dose. See the monograph on tubocurarine chloride.

Like tubocurarine, the methylated derivative is compatible with general anesthetic agents, including the barbiturates employed for this purpose, and is used in conjunction with them to increase skeletal muscle relaxation for certain surgical procedures. See also the general statement on skeletal muscle relaxants.

Dosage.—Dimethyl tubocurarine iodide is administered intravenously in isotonic sodium chloride solution for muscle relaxation

in surgery. The average initial dose is approximately 2 mg. and is injected slowly over a period of 30 to 60 seconds, but the size of the initial dose will be influenced by the type of general anesthetic employed; with cyclopropane, 2 to 4 mg may be required; with ether, 1.5 to 3 mg; with nitrous oxide and thiopental sodium, 3 to 8 mg. Satisfactory relaxation cannot be obtained with initial doses below 1 mg. The initial dose may be expected to provide relaxation for periods ranging from 25 to 90 minutes, or an average of approximately 60 minutes. Supplemental injections of 0.5 to 1 mg may be made as required and indicated by the depth of surgical relaxation. As with all curare preparations, it is important that the user be experienced in the administration of the drug to avoid the dangerous consequences of overdosage. Respiratory paralysis should be treated promptly by artificial respiration with an airway, until the paralysis has receded. Neostigmine methylsulfate solution 1:2,000 in 1 to 2 cc doses, or 1 cc (10 mg) of edrophonium chloride, should be at hand for intravenous administration to combat respiratory depression, but when this is associated with a fall in blood pressure due to excessive curarization, neostigmine methylsulfate may aggravate the condition of shock.

Like other curarelike drugs, dimethyl tubocurarine iodide is contraindicated in patients with respiratory embarrassment, pulmonary disease or serious circulatory impairment and in patients with myasthenia gravis, except as a diagnostic measure.

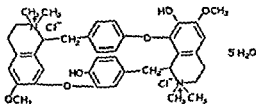
ELI LILLY & COMPANY

Solution Metabine Iodide. 10 cc ampuls. An isotonic salt solution containing 0.5 mg of dimethyl tubocurarine iodide in each cubic centimeter. Preserved with 0.5 per cent phenol.

10 cc. ampuls and 50 cc vials. An isotonic salt solution containing 1 mg of dimethyl tubocurarine iodide in each cubic centimeter. Preserved with 0.5 per cent phenol.

20 cc. ampuls. An isotonic salt solution containing 2 mg. of dimethyl tubocurarine iodide in each cubic centimeter. Preserved with 0.5 per cent phenol.

TUBOCURARINE CHLORIDE-U.S.P.—*d*-Tubocurarine chloride.—The structural formula of tubocurarine chloride may be represented as follows:



Physical Properties.—Tubocurarine chloride occurs as a white or yellowish-white to gray or light tan, odorless, crystalline powder. It melts with slight decomposition at about 270°. One gram of

tubocurarine chloride dissolves in about 40 cc. of water and in about 75 cc. of alcohol. It is insoluble in acetone, in chloroform and in ether.

Actions and Uses.—Tubocurarine chloride is used to reduce the tone or contractile power of skeletal muscle. It is used with light general anesthesia to obtain greater relaxation of the musculature in abdominal surgery, in special surgery of long duration requiring exceptional management and in orthopedic manipulative procedures. It also has been employed to diminish the violence of muscular contractions during metrazol or electric shock therapy and, temporarily, to lessen spasticity due to disease or injury of the central nervous system. Since it aggravates myasthenia gravis symptoms, it has been used in reduced dosage as a diagnostic agent for this condition. See also the general statement on skeletal muscle relaxants.

Dosage.—In conjunction with light surgical anesthesia, premedication should be carried out as usual. The following doses are applicable with general anesthetics *except ether, when only one-third of the recommended dose should be employed.* After induction of light surgical anesthesia, 6 to 9 mg. (40-60 units) of tubocurarine chloride may be given in a single intravenous injection for the required muscular relaxation; an additional 3 to 4.5 mg. (20-30 units) may be given in 3 to 5 minutes and repeated later if necessary. The effect usually appears in 3 to 5 minutes. In overdosage, if ventilation is insufficient, but a patent airway exists, adequate pulmonary exchange may be maintained by periodic compression of the bag of the anesthetic apparatus.

The following table gives the approximate doses of tubocurarine chloride for various types of anesthesia and for the treatment of myasthenia gravis.

to permit training in the voluntary use of muscles, it may be administered intramuscularly. The dose is determined by trial, beginning with 3 mg. (20 units) intramuscularly for each 40 pounds of body weight and gradually increasing the dose until the amount producing the best results is found. As a diagnostic test for myasthenia gravis, 0.3 mg. (2 units) per 40 pounds of body weight is given intravenously, extreme exaggeration of symptoms appears within 2 minutes if myasthenia is present. As soon as a positive reaction is obtained, the curare effect should be antagonized by the intravenous injection of 1 or 2 cc. of neostigmine methylsulfate 1:2,000, combined with 0.6 mg. of atropine sulfate, or 1 cc. (10 mg.) of edrophonium chloride.

The high potency solution of tubocurarine chloride, 15 mg. (100 units) per cubic centimeter never should be injected without dilution because of the danger of overdosage by too rapid administration. Tubocurarine chloride-barbiturate combination anesthesia should not be used in patients with pulmonary disorders, renal dysfunction, liver disease, respiratory depression or obstructive states and myasthenia gravis. In fact, since patients react inde-

permitting resumption of the normal transmission of neuromuscular impulses. Therefore, the drug is useful as an antidote against the peripheral action of curariform agents, either to terminate their therapeutic relaxant effect when it is no longer required or to reverse respiratory muscle paralysis caused by overdosage. Edrophonium chloride does not combat circulatory collapse which sometimes is associated with respiratory depression produced by a central effect of curariform drugs. With extremely large doses, the action of edrophonium becomes curariform and capable of potentiating rather than antagonizing the peripheral paralytic effect of curare. In the presence of apnea, the response to the antidotal action of edrophonium cannot be observed, and there is no clinical guide to effective dosage. For these reasons, the drug should be employed only as a supplement to artificial respiration and oxygen therapy in the treatment of respiratory depression caused by curare overdosage, but, in order to avoid overdosage, edrophonium should be used for this purpose only when some definite sign of voluntary respiration, such as excursion of the diaphragm, can be observed. Under no circumstances should the drug be employed without observing proper precautions in the administration and dosage of curariform agents.

Edrophonium exhibits the parasympathomimetic actions characteristic of neostigmine to some degree, but in the antidotal dosage range it is slightly shorter-acting and produces a lower incidence of side effects. Like the anticholinesterases such as neostigmine, edrophonium prolongs rather than antagonizes the skeletal muscle relaxant action of succinylcholine chloride and should not be used as an antidote for that drug. Increased salivation and bronchiolar spasm have been reported occasionally in patients with asthma, bradycardia and cardiac dysrhythmia in conjunction with electrocardiographic changes in older patients. The drug, therefore, should be employed with caution in bronchial asthma or cardiac disease. Atropine usually relieves such side effects.

Edrophonium chloride also is useful as a diagnostic agent to differentiate between the presence or absence of myasthenia gravis and for the emergency treatment of myasthenic crises. Its action is too short for maintenance therapy of that disease. Because of its shorter action, edrophonium has the advantage over neostigmine as a diagnostic agent of permitting repeated tests on the same patient several times in an afternoon. The diagnostic use of edrophonium is based upon its ability to produce increased muscle strength without fasciculations when administered to patients with myasthenia gravis. In nonmyasthenic patients the drug often produces fasciculations but no increase in strength.

Dosage.—As an antidote for curariform drugs, edrophonium chloride is administered by intravenous injection in doses of 10 mg (1 cc of a solution containing 10 mg per cubic centimeter). Smaller doses of 5 mg each may be adequate for termination of curarization following electroshock therapy. When given to counteract curare overdosage, the effect of each dose on the respiration should be observed carefully before it is repeated,

and artificial ventilation always should be employed. The maximal dose for any one patient should be 30 mg. (\pm 10 mg.). Because the action of edrophonium is brief, it should not be given prior to, or as a prophylactic against, the administration of curariform agents. It should be given only at the time its antidotal effect is needed.

As a diagnostic agent in suspected cases of myasthenia gravis, a 10 mg dose of the drug is injected intravenously. In persons having that disease, increase in muscle strength is observed with maximum improvement occurring within 30 seconds to 3 minutes following injection. In myasthenic crises the drug should be administered by continuous intravenous drip only for the duration of the emergency.

HOFFMANN-LA ROCHE, INC

Solution Tensilon Chloride: 10 cc vials. A solution containing 10 mg. of edrophonium chloride in each cubic centimeter. Preserved with 0.2 per cent sodium sulfite and 0.5 per cent phenol.

U S patent 2,647,924 U S trademark 570,951

NEOSTIGMINE METHYLSULFATE.—See the monograph in the chapter on autonomic drugs

Vitamins

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drates, fats and minerals are essential for the preservation of bodily
well-being and physiologic function. These factors are designated
as vitamins.

The absence of any vitamin from a diet that is satisfactory in other respects leads to the development of a typical syndrome called a "deficiency disease." This type of disease may be as striking in its manifestations as are the results of gross underfeeding (caloric deficiency) or deprivation of essential inorganic elements such as iodine, iron, calcium or phosphorus. Scurvy, for example, can be entirely averted or cured by including in the diet foods that contain vitamin C (ascorbic acid). The prophylactic or remedial agent—the antiscorbutic substance—is a chemical entity, $C_6H_8O_6$.

A vitamin then is a substance essential for maintenance of normal metabolic functions, not synthesized in the human body in normally adequate amounts. Therefore, it must be furnished from an exogenous supply. It is sometimes more labile than the food-stuffs proper and, hence, among the edible products characteristic of the diet which they are required.

Occurring compounds having vitamin activity have been isolated and identified. All of the well-recognized vitamins, except for carotenes, which are precursors of vitamin A, and vitamin B₁₂, are produced commercially in synthetic form.

For convenience the designations vitamins A, B, C and D were used. Scurvy, beriberi, rickets, pellagra and xerophthalmia result from the lack of specific vitamins; the protective or curative substances accordingly were spoken of as the antiscorbutic vitamin (C), the antineuritic vitamin (B₁), the antirachitic vitamin (D), the pellagra-preventing vitamins (mainly nicotinic acid) and the antixerophthalmic vitamin (A). Most of them now have well established chemical names.

Chemical, physical and microbiologic methods now are used for the determination of vitamins in pharmaceutical products, but

of standards for vitamins A, B₁, B₁₂, C, D and E. The international unit for each of these vitamins is defined in terms of the biologic activity of a specific quantity of the respective standard. The United States Pharmacopoeial Convention also distributes prototype standards for these six vitamins and, in addition, reference standards for several other vitamins. U.S.P. units and international units are identical in value.

It is possible to specify vitamin requirements within narrow limits. A properly selected diet ordinarily affords an adequate supply of vitamins. Furthermore, it is difficult to find evidence of frank deficiency diseases in the adult population of this country. However, restrictions leading to unbalanced diet may cause a shortage of some of the vitamins. The situation almost always can be corrected by prescription of appropriate foods. Occasionally, and particularly with infants, a correction may be secured more effectively by the administration of products rich in the desired vitamin; for example, cod liver oil as a dietary adjunct in the prevention or treatment of rickets, and orange juice in the relief of scurvy.

There are still few indications for specific vitamin therapy. Recognition of special vitamin-bearing products applies to unusual concentrations of the desired potent principle and to exceptionally desirable dosage forms. Multivitamin preparations, particularly capsules, have come into extensive use in recent years. In most of these preparations the proportion of vitamins present bears no relation to established therapeutic dosages, nor to normal requirements for the vitamins. The Council on Pharmacy and Chemistry opposes the use of such preparations and recommends for use only multivitamin preparations in which the vitamin content is in proportion to the daily needs. This subject is discussed in a report published in *J.A.M.A.* 119:948 (July 18) 1942.

A deficiency of any food essential leads to retardation of growth. This is true of each of the essential vitamins, but it is equally true of each of the essential amino acids, minerals and energy-yielding compounds.

A person suffering from malnutrition is more susceptible to certain types of infections than the normal individual. But these infections have not been shown to be correlated more closely to specific deficiencies than they are to the organisms to which the body is exposed. Secondary infections are characteristic of conditions resulting from severe vitamin deficiency. The administration of vitamins in excess of bodily needs does not make one more resistant to disease than does the ingestion of quantities just sufficient to meet normal metabolic requirements.

Labels of vitamin preparations which supply in the recommended daily intake not more than three times the minimum daily requirements set forth in regulations under Section 403 (j) of the Food, Drug and Cosmetic Act, must show the proportion of the minimum daily requirements supplied in the recommended daily intake.

Vitamin preparations that supply in each unit (tablet, capsule, etc.) or in the recommended daily intake more than three times the minimum daily requirements set forth in regulations under Section

403 (j) of the Food, Drug and Cosmetic Act are considered acceptable by the Council on Pharmacy and Chemistry if they are advertised only to the physician. To meet the requirements of the Food, Drug and Cosmetic Act with respect to adequate direc-

the label:

STATEMENTS REQUIRED ON MAIN LABEL

For Preparations Supplying More Than Three Times the Minimum Daily Requirements

Quantity of contents:	50 tablets
Common or usual name:	Thiamine Hydrochloride Tablets
Quantity of vitamin in tablets consumed daily:	10 mg.
Adequate directions for use:	Dose: One tablet daily, or as prescribed by the physician. This dosage is in excess of the quantity needed for prevention of thiamine deficiency.
Name and place of business:	John Doe 550 Broad Street Chicago, Illinois

For Preparations Supplying Three Times the Minimum Daily Requirements or Less

Quantity of contents:	100 tablets
Common or usual name:	Thiamine Hydrochloride Tablets
Quantity of vitamin in tablets consumed daily:	1 mg.
Dose:	This is optional
Proportion of minimum daily requirement:	1 tablet will supply the minimum daily requirement for an adult
Name and place of business:	John Doe 550 Broad Street Chicago, Illinois

VITAMIN A

The term "vitamin A" has been applied to several substances and mixtures of these substances that produce a specific demonstrable physiologic effect.

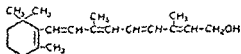
1 A are produced
- substances results

in the formation of various amounts (depending on the species of animal)
 the empirical
 precursor
 species of animals varies.

Evidence for the existence of vitamin A and its role in human nutrition is based on the fact that a characteristic eye disease, usually called xerophthalmia, results from a deficiency of this vitamin. Vitamin A is found in fish liver oils and also is produced synthetically.

The U.S.P. requires that the potency of vitamin A preparations be expressed, on the labels, in U.S.P. units or in metric units referring to the equivalent amount of vitamin A alcohol. The unit for vitamin A is defined as the vitamin A activity of 0.3 mcg of vitamin A alcohol. The Council on Pharmacy and Chemistry has recommended that the marketing of dosage sizes of vitamin A preparations should be limited to capsules, tablets or average fluid doses of 25,000 U.S.P. units or less

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 may be represented as follows.



Physical Properties.—Oleovitamin A is a white to yellowish solid or a yellow to red oily liquid. It is a clear liquid at temperatures above 65°, and it may crystallize on cooling. Oleovitamin A may be nearly odorless or may have a fishy odor but no rancid odor or taste. It is unstable to air and light. Oleovitamin A is insoluble in water and in glycerin. It is soluble in absolute alcohol, and in vegetable oils. It is very soluble in ether and in chloroform.

Actions and Uses.—One of the first clinical symptoms of vitamin A deficiency is night blindness, or nyctalopia. For this type of night blindness vitamin A is a specific. Cases of nyctalopia which do not respond to treatment with vitamin A may be due to contamination "A." The automobile does not

Vitamin A is effective in the treatment of certain types of hyperkeratosis of the skin in persons suffering from severe deficiency of vitamin A.

Vitamin A in excess of normal requirements has not been shown

to be of value in the prevention of colds, influenza and such infections

Evidence does not warrant use of vitamin A in the prevention of the formation of renal calculi in man or in the treatment of hyperthyroidism, anemia, degenerative conditions of the nervous system, sunburn or ulcerative conditions of the skin.

Dosage.—The minimum daily requirements of vitamin A are 1,500 units for infants, 3,000 units for children and 4,000 for adults. Therapeutic dosages should be at least three times these requirements.

While dosages as large as 100,000 and even 200,000 units daily have been used in certain experimental studies, there is no satisfactory evidence that justifies the use of more than 25,000 units a day. Quantities in excess of those actually needed are stored in the liver and the vitamin is available for future use. Doses in excess of 200,000 units a day are injurious to infants.

AMERICAN PHARMACEUTICAL COMPANY, INC.

Capsules Oleovitamin A: Each capsule contains 25,000 U.S.P. units of vitamin A.

BREWER & COMPANY, INC.

Gel-ets Oleovitamin A: Each capsule contains 25,000 U.S.P. units of vitamin A.

IVES-CAMERON COMPANY, DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Capsules Oleo Vitamin A: Each capsule contains 25,000 U.S.P. units of vitamin A derived from fish liver oils

PREMO PHARMACEUTICAL LABORATORIES, INC.

Capsules Vitamin A: Each capsule contains 25,000 U.S.P. units of vitamin A derived from fish liver oils.

WHITE LABORATORIES, INC

Capsules Oleovitamin A: Each capsule contains 25,000 U.S.P. units of vitamin A derived from fish liver oils.

WATER-MISCIBLE VITAMIN A-U.S.P.—Acon (ENDO).—"Water-miscible Vitamin A is vitamin A, in the form of oleovitamin A, rendered water-miscible with the aid of suitable, harmless dispersing agents. The vitamin A activity is not less than 95 per cent that declared on the label. It may contain a flavoring agent." U.S.P.

Actions, Uses and Dosage.—See the monograph on oleovitamin A.

ENDO PRODUCTS, INC.

Acon Vitamin A Capsules: Each capsule contains 25,000 or 50,000 U.S.P. units of vitamin A as the palmitate.

Acon Vitamin A (Water-dispersible) Drops: 30 cc bottles. An aqueous solution containing 25,000 U.S.P. units of vitamin A

(synthetic, palmitate) in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben
U. S. trademark 538,867

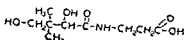
U. S. VITAMIN CORPORATION

Aquasol Vitamin A Drops: 15 and 30 cc bottles An aqueous solution containing 50,000 U.S.P. units of natural vitamin A in each cubic centimeter.
U. S. patent 2,417,299.

VITAMIN B COMPLEX

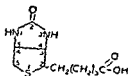
The term vitamin B complex is applied to the group of substances which are constituents of what was formerly called vitamin B. Intensive investigations produce an ever-changing picture of the constituents of the complex. Nine members of the vitamin B complex are being manufactured by synthetic processes. Of these, cyanocobalamin, folic acid, nicotinic acid, pyridoxine, riboflavin and thiamine are discussed in the following pages.

Other members of the group are pantothenic acid and biotin. Pantothenic acid is a factor necessary for the growth of many animals, but its value in human nutrition has not been demonstrated. It is a constituent of an enzyme designated coenzyme A, which may have important metabolic functions. The structural formula of pantothenic acid may be represented as follows.



Biotin combines with a proteinlike substance in raw egg white called "avidin." In suitable diets containing large proportions of raw egg white, the rat or chick develops characteristic skin lesions and growth is retarded. These symptoms can be prevented by ingestion of biotin. The practical significance of these observations is not established because there is evidence that sufficient quantities of biotin for metabolic requirements may be synthesized in the intestinal tract.

The structural formula of biotin may be represented as follows:



In addition to these compounds there are other factors that have been shown to be essential nutrients for a few species of experimental animals. None of these has been shown to have any importance in human nutrition.

The U.S.P. requires that, on the labels, the potency of the various members of the vitamin B complex, with the exception of cyanocobalamin and other B₁₂ preparations, be expressed in milligrams. The potency of cyanocobalamin is expressed in micrograms; the potency of vitamin B₁₂ with intrinsic factor concentrate is expressed in U.S.P. Units (oral). One U.S.P. Unit (oral) is equivalent to not more than 15 mcg. of cyanocobalamin.

The Council on Pharmacy and Chemistry considers that the following types of preparations of the vitamin B complex are useful therapeutically.

1. Mixtures of pure thiamine, riboflavin and nicotinic acid providing in the recommended daily intake: 1 mg. thiamine, 1.5 to 2 mg. riboflavin, 10 mg. nicotinic acid or simple multiples thereof.

2. Dried yeast-U.S.P. having the following minimum vitamin content in each gram: 0.12 mg. thiamine, 0.04 mg. riboflavin and

in (2), to which has been providing for each 1 mg. to 2 mg. of riboflavin and

10 mg. nicotinic acid.

4. A concentrate of the vitamin B complex from brewer's yeast as described in (2), and providing in the recommended daily intake: 1 mg. thiamine (or a simple multiple thereof) and corresponding proportions of other known vitamins of yeast.

5. A concentrate of the vitamin B complex from liver containing not less than 0.25 mg. riboflavin per gram.

6. A concentrate of the vitamin B complex from brewer's yeast fortified with riboflavin and nicotinic acid and providing in the recommended daily intake, 1 mg. thiamine, 1.5 to 2 mg. riboflavin and 10 mg. nicotinic acid, or simple multiples thereof.

7. A concentrate of the vitamin B complex from rice polishings fortified with riboflavin and nicotinic acid and providing in the recommended daily intake: 1 mg. thiamine, 1.5 to 2 mg. riboflavin and 10 mg. nicotinic acid, or simple multiples thereof.

The term "concentrate" or a synonym should not be used for a concentrate containing thiamine if the potency of the product does not exceed 0.075 mg. per gram (or per cubic centimeter), or if it is a natural product that may have been subjected to a process of dehydration.

VITAMIN B COMPLEX.—A concentrated extract of dried brewer's yeast and an extract of corn processed with *Clostridium acetobutylicum*.

Actions and Uses.—Proposed for prophylaxis and treatment of conditions arising from deficiency of the vitamin B complex.

Dosage.—See the monographs on the individual components of the vitamin B complex.

MARVIN R. THOMPSON, INC.

Syrup Vitamin B Complex: 178 and 473 cc. and 3.78 liter bottles. Each cubic centimeter contains 0.3 mg. of thiamine hydrochloride, 0.2 mg. of riboflavin, 0.1 mg. of pyridoxine hydrochloride, 1.4 mg.

of niacin and niacinamide and other vitamin B complex factors extracted from 2 Gm of dried brewer's yeast.

VICO PRODUCTS COMPANY

Syrup Vitamin B Complex: 178 cc bottles. Each cubic centimeter contains 0.3 mg. of thiamine hydrochloride, 0.2 mg. of riboflavin, 0.1 mg. of pyridoxine hydrochloride, 1.4 mg of niacin and niacinamide, and other vitamin B complex factors extracted from 2 Gm of dried brewer's yeast.

U. S. patent 2,193,876

Cyanocobalamin

CYANOCOBALAMIN-U.S.P.—Bavidox (Abbott)—Hamomin (Kirk)—Remetin (Bio-Ramo)—Vibalt (Roerig)—Vitamin B₁₂—"Cyanocobalamin . . . has a purity of not less than 95 per cent, calculated on the dried basis" *U.S.P.*

Physical Properties.—Cyanocobalamin occurs as dark red crystals or as a crystalline powder. One gram dissolves in about 80 cc of water. It is soluble in alcohol but is insoluble in acetone, in chloroform and in ether. Cyanocobalamin is inactivated slowly in solutions of strong acids or alkalis, but in saline solution it withstands autoclaving for 15 minutes at 121°. If kept under sterile conditions, the drug in isotonic saline solution can be stored at room temperature for more than a year without significant loss of therapeutic activity.

Actions and Uses.—Cyanocobalamin possesses hemopoietic activity apparently identical with that of the antianemia factor of liver. However, it has not been established as the complete or essential counterpart of that substance. Studies thus far indicate it to be clinically efficacious in the treatment of pernicious anemia with or without neurologic complications and also in the treatment of tropical and nontropical sprue and nutritional macrocytic anemia resulting from vitamin B₁₂ deficiency. It is effective only in certain cases of megaloblastic anemia of infancy. The drug is useful particularly in the treatment of patients who are sensitive to liver extract. Cyanocobalamin is fully as effective as liver extract in patients with spinal cord lesions associated with pernicious anemia.

Animal experiments have shown no evidence of toxic effects, either local or systemic, from oral or subcutaneous administration of cyanocobalamin, and no toxic reactions in man have been reported.

Dosage.—Cyanocobalamin is extremely potent and, while data are as yet insufficient to warrant exact estimates of the minimum or optimum effective dosage, the minimum is believed to be approximately 1 mcg per day, or multiples of this amount at corresponding intervals, e.g., 35 mcg every 2 weeks. The effectiveness of the dosage may be judged by hematologic findings and altered accordingly. One microgram of the drug is estimated to be about equal biologically to one U.S.P. "injectable" unit of liver extract,

but further study is necessary to determine accurately the comparative clinical potency of these two agents.

The dosages recommended for parenteral administration are as follows. In uncomplicated pernicious anemia, 15 mcg. once or twice a week until remission occurs, then a maintenance dose of 15 mcg. every other week. In pernicious anemia with neurologic complications, 15 to 30 mcg. once or twice a week until remission occurs, then a maintenance dose of 15 mcg. every other week. In sprue, 15 to 30 mcg. once or twice a week will usually induce remission, but 15 mcg. once a week thereafter often is necessary to prevent relapse. In nutritional macrocytic anemia in children or adults, a single dose of 15 mcg. usually is sufficient to produce a favorable initial response, but sometimes it may be necessary to repeat this dose at 2-week intervals to prevent relapse.

Recent studies dealing with oral administration indicate that while satisfactory responses sometimes are obtained when high doses are employed the response is not as consistent or predictable as that achieved by parenteral administration. Usually, it is injected subcutaneously or intramuscularly.

The Council on Pharmacy and Chemistry has recommended that the marketing of dosage sizes of this vitamin should be limited to solutions of a concentration of 10, 20, 30 or 50 mcg. per cubic centimeter.

ABBOTT LABORATORIES

Solution Bevidox Crystalline: 10 cc. vials. An isotonic solution containing 30 mcg. of cyanocobalamin in each cubic centimeter. Preserved with 0.01 per cent benzethonium chloride.

U. S. trademark 538,155.

BIO-INTRASOL LABORATORIES, INC.

Solution Crystalline Vitamin B₁₂ with Benzyl Alcohol 1.5%: 10 and 30 cc. vials. A solution containing either 30 or 50 mcg. of cyanocobalamin in each cubic centimeter.

THE BIO-RAMO DRUG COMPANY

Solution Crystalline Rametin with Benzyl Alcohol 1.5%: 10 cc. vials. A solution containing 10 mcg. of cyanocobalamin in each cubic centimeter.

C. F. KIRK COMPANY

Solution Hemomin with Benzyl Alcohol 1.5%: 30 cc. vials. A solution containing 30 mcg. of cyanocobalamin in each cubic centimeter.

10 and 30 cc. vials. A solution containing 50 mcg. of cyanocobalamin in each cubic centimeter.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Solution Crystalline Vitamin B₁₂: 5 and 10 cc. vials. A saline solution containing 50 mcg. of cyanocobalamin in each cubic centimeter. Preserved with 0.5 per cent phenol.

Solution Crystalline Vitamin B₁₂: 10 cc. vials A saline solution containing 30 mcg. of cyanocobalamin in each cubic centimeter.

RAYMER PHARMACAL COMPANY

Solution Crystalline Vitamin B₁₂. 10 cc vials A saline solution containing 30 or 50 mcg. of cyanocobalamin in each cubic centimeter. Preserved with 0.5 per cent phenol

J. B. ROERIC & COMPANY

Solution Vibalt with Benzyl Alcohol 1.5%: 10 cc vials A solution containing 50 mcg. of cyanocobalamin in each cubic centimeter U. S. trademark 547,447.

WILLIAM H. RORER, INC

Solution Crystalline Vitamin B₁₂. 1 cc ampuls A solution containing 30 mcg. of cyanocobalamin in each cubic centimeter Buffered with sodium acetate and acetic acid

Solution Crystalline Vitamin B₁₂ with Benzyl Alcohol 1.5%: 10 cc vials A solution containing 30 or 50 mcg. of cyanocobalamin in each cubic centimeter. Buffered with sodium acetate and acetic acid

STANDARD PHARMACEUTICAL COMPANY, INC

Solution Crystalline Vitamin B₁₂ with Benzyl Alcohol 2%: 10 cc vials. A saline solution containing 30 or 50 mcg. of cyanocobalamin in each cubic centimeter

THE VITARINE COMPANY, INC

Solution Crystalline Vitamin B₁₂ with Benzyl Alcohol 1.5%: 10 cc vials A saline solution containing 30 or 50 mcg. of cyanocobalamin in each cubic centimeter Preserved with 0.5 per cent chlorobutanol

VITAMIN B₁₂ WITH INTRINSIC FACTOR CONCENTRATE-U.S.P.
—Bifactor (ORGANON)—"Vitamin B₁₂ with Intrinsic Factor Concentrate possesses vitamin B₁₂ activity made more readily absorbable from the gastro-intestinal tract of patients suffering from pernicious anemia by combination with suitable preparations of the mucosa of the stomach or intestine of domestic animals used for food by man. The approximate anti-anemia potency of Vitamin B₁₂ with Intrinsic Factor Concentrate is expressed in U.S.P. Units (oral). The amount constituting 1 U.S.P. Unit (oral) has a Vitamin B₁₂ activity equivalent to that of not more than 15 micrograms of cyanocobalamin and contains not more than 300 milligrams, on the dried basis, of the preparation constituting the intrinsic factor concentrate. Vitamin B₁₂ with Intrinsic Factor Concentrate conforms to all other requirements [for] Anti-anemia Preparations." U.S.P.

Actions and Uses—Vitamin B₁₂, also known as the extrinsic factor, when combined with intrinsic factor concentrate (a partially purified preparation of the intrinsic factor of Castle obtained from stomach tissue of hogs), is effective orally for the treatment of pernicious anemia with and without neurologic complications

It is effective also by virtue of its vitamin B₁₂ content in the treatment of tropical and nontropical sprue, nutritional macrocytic anemia caused by vitamin B₁₂ deficiency and macrocytic anemia of infancy. The *intrinsic factor*, which is lacking in patients with pernicious anemia, increases the efficiency of alimentary absorption of vitamin B₁₂.

Oral administration of vitamin B₁₂ with intrinsic factor concentrate produces an adequate hematopoietic response in patients with pernicious anemia; therefore, it is suitable to replace injectable cyanocobalamin or liver for patients in whom parenteral therapy is difficult or undesirable. Patients should be observed carefully during oral treatment; if expected improvement does not occur, further examination should be made to rule out complicating disorders, such as infection, gastro-intestinal malfunction or undiagnosed malignant disease. In the presence of any such complication, the dosage may need to be increased or abandoned in favor of injection therapy with cyanocobalamin or liver.

Vitamin B₁₂ with intrinsic factor concentrate is fairly stable in dry form, but until more is known regarding the keeping qualities of the intrinsic factor, the mixture should be protected from moisture, light and heat above 45°. The mixture has not been reported to produce any toxic effects. The possibility of gastro-intestinal allergy to hog protein, from which the intrinsic factor is derived, should be borne in mind.

Dosage.—Vitamin B₁₂ with intrinsic factor concentrate is administered orally. The potency is expressed in terms of the U.S.P. oral unit of hematopoietic activity, assigned on the basis of clinical assays submitted to the U.S.P. Anti-Anemia Preparations Advisory Board. The declaration of the amount of cyanocobalamin present in preparations of the mixture is excluded to avoid the misleading implication that this represents additional hematopoietic activity in excess of the labeled unitage.

The average daily dosage for the treatment of pernicious and related macrocytic anemias is 1 U.S.P. oral unit daily, in two divided doses of 0.5 unit each before the morning and evening meals. In severe cases, a more rapid response may be achieved with an initial daily dosage of 2 U.S.P. oral units, also given twice daily in equally divided doses for the first 1 or 2 weeks of therapy. Reticulocyte values usually rise to peak levels within 5 to 12 days. Values for other formed elements of the blood approach normal within 8 to 10 weeks. Megaloblastic bone marrow may return to normal within a few days. Neurologic complications usually are relieved within a period of 1 to 12 weeks, depending on their duration and the intensity of the therapy.

ORGANON, INC.

Tablets Bifacron: Each tablet contains the equivalent of 0.5 U.S.P. oral unit.

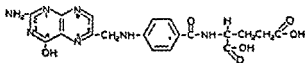
U. S. trademark 566,740.

Folic Acid

Folic acid, a compound widely distributed in foods, is also known by the chemical name pteroylglutamic acid. Only a small portion of the folic acid found in many foods occurs in the free form and it is not yet clear to what extent the combined forms can be utilized by man. The combined forms differ chemically from free folic acid in that they contain additional molecules of glutamic acid and they may be rendered active after hydrolysis with suitable enzymes or acids.

Although folic acid may restore to normal the blood of patients with pernicious anemia, it never should be used alone in the treatment of this disease because it is ineffective in the control of the neurologic symptoms. The substance is specific in the control of certain megaloblastic anemias of infancy and of pregnancy. It is effective in the treatment of most cases of sprue and nutritional macrocytic anemia.

FOLIC ACID—U.S.P.—Folvite (LEDERLE)—Pteroylglutamic acid—N-[4-[(2-amino-4-hydroxy-6-pteridyl)methylamino]benzoyl] glutamic acid—"Folic Acid contains not less than 98 per cent of $C_{19}H_{19}N_7O_6$ calculated to the anhydrous basis" U.S.P. The structural formula of folic acid may be represented as follows:



Physical Properties.—Folic acid is a yellow or yellowish-orange, odorless, crystalline powder. It is insoluble in water, alcohol or the usual organic solvents. It is soluble in dilute solutions of alkali hydroxides and their carbonates and is moderately soluble in hot, diluted hydrochloric or sulfuric acid.

Actions and Uses.—Folic acid produces a response of the blood, similar to that obtained with liver extract, in pernicious anemia, sprue and nutritional macrocytic anemia in man, and in experimental macrocytic anemias due to dietary deficiencies in monkeys, growing chicks and in fish. It also controls the diarrhea in sprue, but does not prevent or cause improvement in the spinal cord lesions in pernicious anemia; these are helped by liver extract. Therefore, in the treatment of pernicious anemia, folic acid should be used only as an adjunct to treatment with liver or cyanocobalamin.

Dosage.—Orally, 5 to 15 mg. daily. Folic acid may be administered by intramuscular injection, but in ordinary cases there is no advantage.

AMERICAN PHARMACEUTICAL COMPANY, INC.

Tablets Folic Acid: 5 mg.

THE EVRON COMPANY, INC.

Tablets Folic Acid: 5 mg.

KEITH-VICTOR PHARMACAL COMPANY

Tablets Folic Acid: 5 mg.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

Elixir Folvite: 125 cc. bottles. An elixir containing 1.25 mg. of folic acid in each cubic centimeter.

Tablets Folvite: 5 mg.

U. S. patent 2,443,165.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Folic Acid: 5 mg.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Folic Acid: 5 mg.

REXALL DRUG COMPANY

Tablets Folic Acid: 5 mg.

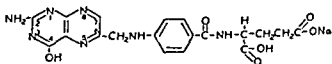
THE UFJOHN COMPANY

Tablets Folic Acid: 5 mg.

WALKER LABORATORIES, INC.

Tablets Folic Acid: 5 and 10 mg

water for injection prepared with the aid of sodium hydroxide or sodium carbonate. It contains not less than 95 per cent and not more than 110 per cent of the labeled amount of $C_{19}H_{19}N_7O_6$ U.S.P. The structural formula of sodium folate may be represented as follows:



Physical Properties.—Sodium folate in solution is a clear, mobile yellow to orange-yellow liquid. In a concentration equivalent to 15 mg. of folic acid per cubic centimeter it has a pH between 8.5 and 11.0.

Actions and Uses.—Sodium folate possesses the activity of folic acid and is preferred when parenteral therapy is indicated.

Dosage.—See the monograph on folic acid.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

Solution Sodium Folvite: 1 cc ampuls A solution containing 15 mg. of sodium folate in each cubic centimeter.

Solution Sodium Folvite with Benzyl Alcohol 1.5%: 10 cc vials A solution containing 15 mg. of sodium folate in each cubic centimeter.

Nicotinic Acid and Nicotinamide

Nicotinic acid ($C_6H_5O_2N$) and nicotinamide ($C_6H_6ON_2$) are of fundamental importance in the treatment of pellagra. The terms niacin and niacinamide, now are recognized officially as synonyms for these chemical names.

The Council on Pharmacy and Chemistry has recommended that the marketing of dosage sizes for these substances should be limited to tablets of 25, 50 and 100 mg. For solutions of nicotinamide, concentrations of 25, 50 or 100 mg. per cubic centimeter are recommended. Solutions of nicotinic acid are considered unnecessary.

NICOTINAMIDE-U.S.P.—Nicotinic Acid Amide—Niacinamide—"Nicotinamide, dried over sulfuric acid for 4 hours, contains not less than 98.5 per cent of $C_6H_6N_2O$ " U.S.P. The structural formula of nicotinamide may be represented as follows:



Physical Properties—Nicotinamide occurs as a white, crystalline powder, nearly odorless and of bitter taste. One gram dissolves in about 1 cc. of water, in about 15 cc. of alcohol and in about 10 cc. of glycerin, at 25°.

Actions and Uses—See the monograph on nicotinic acid. For parenteral use nicotinamide is preferred to nicotinic acid. Nicotinamide does not produce flushing.

Dosage—See the monograph on nicotinic acid.

ABBOTT LABORATORIES

Solution Nicotinamide: 2 cc ampuls A solution containing 50 mg. of nicotinamide in each cubic centimeter.

Tablets Nicotinamide: 50 and 100 mg.

AMERICAN PHARMACEUTICAL COMPANY, INC.

Tablets Nicotinamide: 50 and 100 mg.

BREWER & COMPANY, INC.

Solution Niacinamide: 10 cc vials A solution containing 100 mg. of nicotinamide in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

COLE CHEMICAL COMPANY

Tablets Niacinamide: 100 mg.

THE DRUG PRODUCTS COMPANY, INC.

Pulvoids Nicotinamide: 50 mg.

Hyposols Solution Nicotinamide: 10 cc. vials. A solution containing 50 mg of nicotinamide in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

THE EYRON COMPANY, INC.

Tablets Nicotinamide: 25, 50 and 100 mg.

FLINT, EATON & COMPANY

Tablets Nicotinamide: 50 mg.

IVES-CAMERON COMPANY, DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Tablets Nicotinic Acid Amide: 100 mg.

KEITH-VICTOR PHARMACAL COMPANY

Tablets Niacinamide: 25, 50 and 100 mg.

MERCK & CO., INC.

Powder Niacinamide: 25, 125 and 500 Gm. and 1 Kg. bottles.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Niacinamide: 50 and 100 mg.

U. S. VITAMIN CORPORATION

Solution Niacinamide: 2 cc. ampuls. A solution containing 50 mg of nicotinamide in each cubic centimeter.

Tablets Niacinamide: 25, 50 and 100 mg.

THE UPJOHN COMPANY

Solution Nicotinic Acid Amide: 10 cc. vials. A solution containing 100 mg of nicotinamide in each cubic centimeter. Preserved with 5 mg chlorobutanol.

Tablets Nicotinic Acid Amide: 50 and 100 mg.

THE VALE CHEMICAL COMPANY, INC.

Tablets Nicotinamide: 50 mg.

WALKER LABORATORIES, INC.

Tablets Niacinamide: 25, 50 and 100 mg

WARREN-TEED PRODUCTS COMPANY

Tablets Nicotinamide: 50 mg.

NICOTINIC ACID-U.S.P.—Niacin.—“Nicotinic Acid, dried at 105° for 1 hour, contains not less than 99.5 per cent of $C_6H_5NO_2$ ”

U.S.P. The structural formula of nicotinic acid may be represented as follows:



Physical Properties.—Nicotinic acid is a white, odorless, crystalline powder. It is soluble in water, in alcohol and in solutions of alkali carbonates. It occurs in various plant and animal tissues but apparently cannot be synthesized by animals.

Actions and Uses.—Nicotinic acid and nicotinamide are recognized as specifics only in the treatment of pellagra. Their administration in appropriate doses leads to the disappearance of all alimentary, dermal and other lesions characteristic of the disease, to a return to normal of the porphyrin and porphyrinlike pigments of the urine and to a profound improvement in the mental symptoms which result from inadequate intake of nicotinic acid and nicotinamide. These compounds are without influence upon the polyneuritis so frequently observed in pellagrous patients. In such cases it may be necessary to ensure adequate intake of thiamine hydrochloride.

Administration of large doses of nicotinic acid produces flushing of the face and neck sometimes associated with an unpleasant sensation, but the reaction is transient and apparently harmless. The effect is not observed following the administration of nicotinamide.

Dosage.—For infants, the recommended intake of nicotinic acid is 4 mg. daily. This recommended intake increases with age to 13 to 17 mg. daily between the ages of 13 and 20. Adults should receive 12 to 18 mg. daily. During pregnancy and lactation, 15 mg. daily is recommended. The dose for therapeutic purposes varies with the severity of the deficiency and, possibly, with other as yet unknown factors. The maximum quantity to be recommended is 500 mg. per day, given in ten doses of 50 mg. each.

ABBOTT LABORATORIES

Tablets Nicotinic Acid: 50 and 100 mg.

AMERICAN PHARMACEUTICAL COMPANY, INC.

Tablets Nicotinic Acid: 25, 50 and 100 mg.

THE BOWMAN BROS. DRUG COMPANY

Tablets Nicotinic Acid: 50 mg.

THE EVRON COMPANY, INC.

Tablets Niacin: 25, 50 and 100 mg.

IVES-CAMERON COMPANY, DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Tablets Nicotinic Acid: 50 and 100 mg.

KEITH-VICTOR PHARMACAL COMPANY

Tablets Niacin: 25, 50 and 100 mg.

MERCK & Co, INC.

Powder Niacin: 25, 125 and 500 Gm bottles.

THE Wm. S. MERRELL COMPANY

Tablets Nicotinic Acid: 50 mg.

NATIONAL DRUG COMPANY

Tablets Nicotinic Acid: 50 and 100 mg.

PARKE, DAVIS & COMPANY

Tablets Nicotinic Acid: 50 and 100 mg.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Niacin: 25 mg.

REXALL DRUG COMPANY

Tablets Nicotinic Acid: 50 and 100 mg.

U. S. VITAMIN CORPORATION

Tablets Niacin: 25, 50 and 100 mg.

THE UPJOHN COMPANY

Tablets Nicotinic Acid: 50 and 100 mg

THE VALE CHEMICAL COMPANY, INC.

Tablets Niacin: 50 mg.

WALKER LABORATORIES, INC

Tablets Nicotinic Acid: 25, 50 and 100 mg.

WARREN-TEED PRODUCTS COMPANY

Tablets Niacin: 50 mg.

Pyridoxine

(Vitamin B₆)

Pyridoxine, pyridoxal and pyridoxamine are naturally-occurring compounds which have the biologic activity attributed to vitamin B₆. Pyridoxine apparently is converted into pyridoxal, a substance identified as a constituent of an enzyme system that plays a role in the metabolism of amino acids.

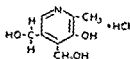
In a critical study and in a few clinical cases it was observed that convulsions and hypochromic anemia developed in pyridoxine-deficient infants. In another experiment the pyridoxine antagonist desoxypyridoxine was administered to adult subjects while they were maintained on a diet deficient in the vitamins of the B complex. Skin and oral lesions resembling those occurring in riboflavin and niacin deficiency developed. Administration of the vitamin B complex devoid of pyridoxine did not improve the condition but the lesions responded promptly to pyridoxine. Epileptiform convulsions were observed in 1952 and 1953 in infants who were fed

exclusively a commercially prepared liquid milk infant formula compounded to simulate mother's milk. This product was found to have an unusually low vitamin B₆ content. The hyperirritability and recurrent seizures, unassociated with other signs of illness, disappeared promptly when the diet was changed or when pyridoxine hydrochloride was administered.

Pyridoxine has some value in the treatment of irradiation sickness. The mechanism of this effect has not been established. Pyridoxine also may be of value in the treatment of nausea and vomiting of pregnancy, but it is not effective in all cases and should be used only as an adjunct to other control measures.

The Council on Pharmacy and Chemistry has recommended that the marketing of dosage sizes of this vitamin should be limited to tablets containing not more than 25 mg and to solutions of a concentration not to exceed 25 mg per cubic centimeter.

PYRIDOXINE HYDROCHLORIDE-U S P — *Beadox Hydrochloride* (Paxto) — 2-Methyl-3-hydroxy-4,5-di-(hydroxymethyl)pyridine hydrochloride — Vitamin B₆ hydrochloride — The structural formula of pyridoxine hydrochloride may be represented as follows



Physical Properties—Pyridoxine hydrochloride is a white, odorless, crystalline powder which melts with decomposition between 200 and 212°. In the crystalline state it is reasonably stable to light and air. Acidic solutions of pyridoxine hydrochloride are stable and may be heated for 30 minutes at 120° without decomposition. One part is soluble in 4.5 parts of water and 100 parts of alcohol; it is sparingly soluble in acetone and practically insoluble in ether. Aqueous solutions are acidic. A solution containing 10 mg per cubic centimeter has a pH of about 3.

Actions and Uses—Pyridoxine hydrochloride may be of value as an adjunct in the treatment of nausea and vomiting of pregnancy and in irradiation sickness.

Dosage—Pyridoxine hydrochloride is administered orally or parenterally but should be injected only when the oral route is not feasible, as in the presence of nausea and vomiting, or whenever adequate absorption by the oral route is doubtful. Solutions containing 10 or 25 mg per cubic centimeter are adequate for intramuscular injection; intravenous administration of such concentrations is not necessary and may be undesirable. When long-term parenteral alimentation is necessary, pyridoxine should be included in the infusions.

Insufficient information is available with respect to effective dosages of vitamin B₆ to warrant setting up definite dosage recommendations. Quantities ranging from 25 to 100 mg daily have been used in most of the clinical studies involving nausea and vomiting of pregnancy and irradiation sickness. However, in none

of these studies was there an attempt to establish the minimum effective therapeutic dose. Studies with experimental animals show that the requirement for vitamin B₆ is essentially the same as for thiamine. If the human requirement is approximately 1 mg. a day, therapeutic dosages of the order of 5 to 10 mg. daily would be indicated.

ABBOTT LABORATORIES

Solution Pyridoxine Hydrochloride: 2 cc. ampuls. A solution containing 25 mg. of pyridoxine hydrochloride in each cubic centimeter.

Tablets Pyridoxine Hydrochloride: 25 mg.

AMERICAN PHARMACEUTICAL COMPANY

Tablets Pyridoxine Hydrochloride: 10 and 25 mg.

ENDO PRODUCTS, INC.

Solution Pyridoxine Hydrochloride: 1 cc. ampuls. A solution containing 25 mg. of pyridoxine hydrochloride in each cubic centimeter

IVES-CAMERON COMPANY, DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Tablets Pyridoxine Hydrochloride: 25 mg

MERCK & CO., INC.

Powder Pyridoxine Hydrochloride: 1, 5, 25, 100 and 500 Gm. bottles.

U. S. trademark 377,657.

E. S. MILLER LABORATORIES, INC.

Tablets Pyridoxine Hydrochloride: 10 mg.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Pyridoxine Hydrochloride: 5 and 25 mg.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Beadox Hydrochloride: 10 and 25 mg.

U. S. VITAMIN CORPORATION

Tablets Pyridoxine Hydrochloride: 25 mg.

THE UPJOHN COMPANY

Tablets Pyridoxine Hydrochloride: 10 mg.

THE VALE CHEMICAL COMPANY, INC.

Tablets Pyridoxine Hydrochloride: 10 mg.

Riboflavin

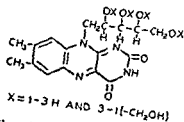
(Vitamin B₂)

Riboflavin, the empirical formula of which is C₁₇H₂₀N₄O₆, was

known formerly as vitamin G, vitamin B₂ or lactoflavin. The chemical nature of the vitamin was established in 1935.

The Council on Pharmacy and Chemistry has recommended that the marketing of dosage sizes of riboflavin preparations should be limited to tablets of 1, 2, 5 and 10 mg, and to solutions of a concentration of 0.2 mg. per cubic centimeter or higher.

METHYLOL RIBOFLAVIN.—Hyflavin (ENDO) — A mixture of methylol derivatives of riboflavin formed by the action of formaldehyde on riboflavin in weakly alkaline solution. The number of methylol groups formed in the ribityl moiety varies from one to three. The structural formula of methylol riboflavin may be represented as follows



Physical Properties.—Methylol riboflavin is an orange to yellow, hygroscopic powder. It is almost odorless or has a slight odor of formaldehyde. It is soluble in water and practically insoluble in alcohol, benzene, chloroform and ether. It is dextrorotatory. The pH of a 10 per cent solution is between 6.7 and 7.9. The dry powder is unstable. It loses its biologic activity in the course of several months with the liberation of formaldehyde and the partial formation of products practically insoluble in water.

Actions and Uses.—Methylol riboflavin possesses the activity of riboflavin and is preferable for parenteral therapy.

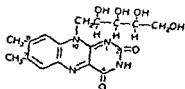
Dosage.—See the monograph on riboflavin.

ENDO PRODUCTS, INC.

Solution Hyflavin with Benzyl Alcohol 2%: 1 cc ampuls and 10 cc vials. A solution containing the equivalent of 10 mg riboflavin in each cubic centimeter.

U. S. trademark 434,874.

RIBOFLAVIN-U.S.P.—Lactoflavin—Vitamin B₂—Vitamin G—“Riboflavin, dried at 105° for 2 hours, contains not less than 98 per cent of C₁₇H₂₀N₄O₆.” U.S.P. The structural formula of riboflavin may be represented as follows.



Physical Properties.—Riboflavin occurs as an orange-yellow, crystalline powder of a slight odor. When dry, it is not appreciably affected by diffused light, but in solution, especially in the presence of alkalis, it deteriorates on exposure to light. One gram dissolves in about 10,000 cc. of water at 25° but is more soluble in a physiologic solution of sodium chloride. It is less soluble in alcohol but very soluble in dilute alkalis.

Actions and Uses.—Riboflavin is a specific in the treatment of certain characteristic lesions of the tongue, the lips and the face. The symptoms may be described briefly as follows: A glossitis may be observed before other signs of riboflavin deficiency occur. As the deficiency progresses, the lips become reddened, then shiny and denuded, with maceration and fissuring of the angles of the mouth (cheilosis). Frequently, seborrheic follicular keratoses occur at the nasolabial folds and even over the nose and forehead.

Riboflavin deficiency is responsible for certain ocular manifestations characterized by itching, burning and a sensation of roughness of the eyes (keratitis), accompanied by mild photophobia. The anatomic changes may vary from a superficial invasion of the cornea by capillaries to an extensive vascular proliferation, with or without infiltration, opacity and exudate formation.

Riboflavin also may be used for the alleviation of symptoms of riboflavin deficiency encountered in other diseases, notably pellagra.

Dosage.—For infants, the recommended intake of riboflavin is 0.6 mg. daily. The allowance increases to 2 to 2.5 mg. daily between the ages of 13 and 20 years. Adults should ingest 1.5 to 1.8 mg. daily. The requirement during pregnancy and lactation is higher. When riboflavin is used therapeutically the dosage varies from 2 to 10 mg. per day depending upon the severity of the deficiency. No side effects have been noticed following the clinical administration of relatively large doses. The vitamin is equally effective whether administered orally or parenterally.

ABBOTT LABORATORIES

Tablets Riboflavin: 5 and 10 mg.

AMERICAN PHARMACEUTICAL COMPANY, INC.

Tablets Riboflavin: 5 and 10 mg.

ENDO PRODUCTS, INC.

Tablets Riboflavin: 5 mg.

THE EVRON COMPANY, INC.

Tablets Riboflavin: 5 and 10 mg.

HART DRUG CORPORATION

Tablets Riboflavin: 5 and 10 mg.

IVES-CAMERON COMPANY, DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Tablets Riboflavin: 5 and 10 mg.

KEITH-VICTOR PHARMACAL COMPANY
Tablets Riboflavin: 5 and 10 mg

MERCK & Co, Inc.
Powder Riboflavin: 1, 5, 25 and 100 Gm bottles

PREMO PHARMACEUTICAL LABORATORIES, INC.
Tablets Riboflavin: 1, 2, 5 and 10 mg.

PHYSICIANS' DRUG & SUPPLY COMPANY
Tablets Riboflavin: 2 and 5 mg.

U. S. VITAMIN CORPORATION
Tablets Riboflavin: 1 and 5 mg.

THE UPJOHN COMPANY
Tablets Riboflavin: 5 mg

THE VALE CHEMICAL COMPANY, INC.
Tablets Riboflavin. 1 and 5 mg

WALKER LABORATORIES, INC.
Tablets Riboflavin: 1, 5 and 10 mg

Thiamine

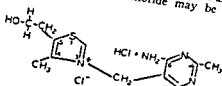
(Vitamin B₁)

This vitamin is of fundamental importance in beriberi. The pure compound was first isolated in 1926. Since that time its chemical constitution has been established and now it is manufactured synthetically. Usually, it is marketed as the hydrochloride.

The Council on Pharmacy and Chemistry has recommended that the marketing of dosage sizes of this vitamin should be limited to tablets of 0.5, 1, 3, 5 or 10 mg, and concentrations of solutions to 1, 5 or 10 mg per cubic centimeter. Dosage forms for parenteral administration in containers larger than 10 cc are considered unnecessary.

THIAMINE HYDROCHLORIDE-U.S.P.—Aneurine Hydrochloride

—Thiamine chloride—Vitamin B₁ hydrochloride—Vitamin B₁—
"Thiamine Hydrochloride, dried at 105° for 2 hours, contains not
less than 98 per cent of C₁₂H₁₇ClN₄OS HCl" U.S.P. The struc-
tural formula of thiamine hydrochloride may be represented as
follows



Physical Properties.—Thiamine hydrochloride occurs as small,

white crystals or as a crystalline powder, having a slight, characteristic odor. One gram dissolves in about 1 cc. of water and in about 100 cc. of alcohol at 25°. It is soluble in glycerin.

Actions and Uses.—Thiamine is of value in correcting and preventing beriberi. This disease with its nervous and cardiovascular manifestations is due primarily to an insufficient supply of thiamine. It is probable that in the majority of instances of human beriberi there are also deficiencies of food constituents other than thiamine. Probably there are conditions that could be designated as "latent beriberi"; it does not seem wise at this time to formulate a definite statement covering such conditions other than that below concerning beriberi heart.

Thiamine is of value in correcting and preventing anorexia of dietary origin only if the fault of the diet is lack of thiamine.

The administration of thiamine in excess of that present in the

normal diet may be administered when there are specific conditions such as neuritis of pellagra, this vitamin may be of value in the treatment of these conditions.

Thiamine is effective in re-establishing the normal function of the cardiovascular system if the dysfunction was caused by thiamine deficiency. Evidence is lacking that thiamine is effective in any other type of heart disease. At times organic heart disease and beriberi heart coexist. Administration of thiamine is justified in these patients.

Thiamine requirement is increased when there is greatly augmented metabolism such as occurs in febrile conditions, hyperthyroidism or vigorous muscular activity.

Dosage.—For infants the recommended daily intake of thiamine hydrochloride is 0.4 mg. The allowance increases to 1.3 to 1.7 mg. daily between the ages of 13 and 20 years. Adults should receive 1 to 1.8 mg. daily. In the well-balanced diet the thiamine requirement should be obtained from the food. Evidence on which to base dosages in the treatment of acute deficiencies is meager. Doses of the order of 10 mg. in some instances.

Thiamine is available in the form of tablets, capsules, and injections. In the treatment of acute deficiencies, the administration of highly potent solutions may cause anaphylactic shock.

Thiamine is available in the form of tablets, capsules, and injections. In the treatment of acute deficiencies, the administration of highly potent solutions may cause anaphylactic shock.

ABBOTT LABORATORIES

Tablets Thiamine Hydrochloride: 3, 5 and 10 mg.

AMERICAN PHARMACEUTICAL COMPANY, INC.

Tablets Thiamine Hydrochloride: 5 and 10 mg.

THE BOWMAN BROS. DRUG COMPANY

Tablets Thiamine Hydrochloride: 5 and 10 mg.

BOYLE & COMPANY

Tablets Thiamine Hydrochloride: 10 mg

COLE CHEMICAL COMPANY

Solution Thiamine Hydrochloride: 475 cc and 3 78 liter bottles
A solution containing 0.5 and 1 mg of thiamine hydrochloride in each cubic centimeter.

Tablets Thiamine Hydrochloride: 1, 3 and 5 mg

THE DRUG PRODUCTS COMPANY, INC.

Pulvoids Thiamine Hydrochloride: 1 and 3 mg

Solution Thiamine Hydrochloride 1 cc ampul hypodermics. A solution containing 10 mg of thiamine hydrochloride in each cubic centimeter.

10 cc hypodermic vials A solution containing 10 mg of thiamine hydrochloride in each cubic centimeter Preserved with 0.5 per cent chlorobutanol.

R. E. DWIGHT & COMPANY

Tablets Thiamine Hydrochloride: 5 and 10 mg.

ENDOCRINE COMPANY

Solution Thiamine Hydrochloride Drops (Oral) 30 and 118.3 cc bottles A solution containing 50 mg of thiamine hydrochloride in each cubic centimeter.

ENDO PRODUCTS, INC.

Solution Thiamine Hydrochloride: 1 cc ampuls and 10 cc vials A solution containing 10 mg of thiamine hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Tablets Thiamine Hydrochloride: 1, 3 and 5 mg

THE EVRON COMPANY, INC

Tablets Thiamine Hydrochloride. 5 and 10 mg

FLINT, EATON & COMPANY

Solution Thiamine Hydrochloride 1 cc ampuls A solution containing 10 mg. of thiamine hydrochloride in each cubic centimeter

Tablets Thiamine Hydrochloride. 1, 5 and 10 mg

GOLD LEAF PHARMACAL COMPANY

Solution Thiamine Hydrochloride 10 cc vials A solution containing 10 mg of thiamine hydrochloride in each cubic centimeter Preserved with 0.5 per cent chlorobutanol

Tablets Thiamine Hydrochloride: 1, 5 and 10 mg.

HORTON & CONVERSE

Tablets Thiamine Hydrochloride: 5 and 10 mg

IVES-CAMERON COMPANY, DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

Tablets Thiamine Hydrochloride: 5 and 10 mg.

KEITH-VICTOR PHARMACAL COMPANY

Tablets Thiamine Hydrochloride: 5 and 10 mg.

LINCOLN LABORATORIES, INC.

Lyophilized Thiamine Hydrochloride: 10 cc. vials. Each vial contains 0.1 Gm. of thiamine hydrochloride. Reconstitution with accompanying diluent gives a solution containing 10 mg of thiamine hydrochloride in each cubic centimeter. The diluent contains 0.16 per cent methylparaben and 0.04 per cent propylparaben as preservatives.

Tablets Thiamine Hydrochloride: 10 mg.

MERCK & CO., INC.

Powder Thiamine Hydrochloride: 5, 25 and 100 Gm. bottles.

THE W. S. MERRELL COMPANY

Tablets Thiamine Hydrochloride: 5 and 10 mg

E. S. MILLER LABORATORIES, INC.

Tablets Thiamine Hydrochloride: 5 and 10 mg.

NATIONAL DRUG COMPANY

Tablets Thiamine Hydrochloride: 1 mg.

NION CORPORATION

Tablets Thiamine Hydrochloride: 10 mg.

PASADENA RESEARCH LABORATORIES, INC.

Solution Thiamine Hydrochloride: 10 cc. vials. A solution containing 10 mg. of thiamine hydrochloride in each cubic centimeter. Preserved with 0.35 per cent chlorobutanol.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Thiamine Hydrochloride: 1, 3, 5 and 10 mg.

J. B. ROERIC & COMPANY

Solution Thiamine Hydrochloride: 10 cc vials A solution containing 10 mg of thiamine hydrochloride in each cubic centimeter. Preserved with 0.35 per cent chlorobutanol.

WILLIAM H. RORER, INC.

Tablets Thiamine Hydrochloride: 5 mg.

E. R. SQUIBB & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION

Tablets Thiamine Hydrochloride: 3, 5 and 10 mg.

SUCCESS CHEMICAL COMPANY, INC.

Tablets Thiamine Hydrochloride: 10 mg.

SUTLIFF & CASE COMPANY, INC.

Tablets Thiamine Hydrochloride: 1 mg

U. S. VITAMIN CORPORATION

Tablets Thiamine Hydrochloride. 5 and 10 mg

THE UPJOHN COMPANY

Tablets Thiamine Hydrochloride: 5 and 10 mg.

THE VALE CHEMICAL COMPANY, INC.

Tablets Thiamine Hydrochloride: 1, 3, 5 and 10 mg.

VANPELT & BROWN, INC.

Tablets Thiamine Hydrochloride. 5 and 10 mg

WALKER LABORATORIES, INC.

Solution Thiamine Hydrochloride (*Oral*): 15 and 60 cc bottles
A solution containing 5 mg of thiamine hydrochloride in each
cubic centimeter. Preserved with 0.1 per cent methylparaben.

Tablets Thiamine Hydrochloride: 1, 3, 5 and 10 mg.

WINTHROP-STEARNES, INC.

Tablets Thiamine Hydrochloride: 5 and 10 mg

Mixed Vitamin B Components

TRIASYN B-N.F.—"Triasyn B Capsules [and Tablets] contain

ascorbic acid. See the monographs on these components.

BREWER & COMPANY, INC.

Gels Triasyn B: Each capsule contains 2 mg of thiamine hydrochloride, 3 mg. of riboflavin and 20 mg. of nicotinamide

VITAMIN C

Ascorbic acid (vitamin C) is present in such foods as fresh vegetables and fruits, yet entirely lacking in such others as the common cereals and grains. All pure ascorbic acid preparations used in pharmaceuticals are of the same quality.

Ascorbic acid is essential for the normal development of the blood vessels, however, on roentgenologic evidences in the long bones, the blood level of ascorbic acid and the clinical picture and history of the disease. Dental caries, pyorrhea, certain gum infections, anorexia, anemia,

value in these symptomatic conditions *only when* they are the consequences of a deficiency of ascorbic acid or when there is a pathologic interference with assimilation of the amount necessary for the preservation of health. This latter situation is rare.

Because ascorbic acid is a dietary essential its administration in concentrated form is of value in conditions where difficulty is encountered in introducing it orally or in utilizing ordinary foods in the usual way. Generally, it is administered in the form of an ascorbic-acid-carrying juice. It may be administered intramuscularly in concentrated form as sodium ascorbate when persistent vomiting, diarrhea or other conditions prevent the utilization of proper amounts taken orally.

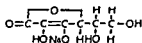
In planning diets for infants who do not receive breast milk, and for small children, it is advisable to make special provision for a source of ascorbic acid such as orange juice because the concentration of ascorbic acid in fresh cow's milk is only about one-fourth of the concentration in mother's milk and because in most foods the vitamin content is reduced during cooking or processing.

Dosage.—The recommended daily intake of ascorbic acid for an infant is approximately 30 mg. Recommended levels of intake increase through childhood to 80 to 100 mg daily between the ages of 13 and 20 years. For adults, the recommended daily intake is 70 to 75 mg. During pregnancy and lactation, the allowance may be as high as 100 or 150 mg.

When pharmaceutical preparations are prescribed, the protective dose for infants is 10 mg. daily, and the therapeutic dose is 30 to 50 mg. daily. The protective dose for adults is 25 mg. daily and the therapeutic dose is 100 to 150 mg. daily. Each 1 mg. is equivalent to 20 international units of vitamin C. No evidence exists that tenfold increases exert detrimental effects.

The U.S.P. requires that the potency of ascorbic acid preparations be expressed, on the labeling, in milligrams. The Council on Pharmacy and Chemistry has recommended that the marketing of dosage sizes of ascorbic acid preparations should be limited to 10, 25, 50 and 100 mg. tablets, and to concentrations of not more than 100 mg per cubic centimeter in containers of less than 10 cc.

SODIUM ASCORBATE.—**ASCORBIC ACID INJECTION-U.S.P.**—"Ascorbic Acid Injection is a sterile solution of ascorbic acid in water for injection prepared with the aid of sodium hydroxide, sodium carbonate or sodium bicarbonate. It contains not less than 95 per cent and not more than 115 per cent of the labeled amount of $C_6H_8O_6$." *U.S.P.* The *U.S.P.* requires that potency of ascorbic acid be expressed in terms of ascorbic acid on labels. The structural formula of sodium ascorbate may be represented as follows.



Action, Uses and Dosage.—Sodium ascorbate possesses the activity of ascorbic acid and is preferred when intramuscular therapy is indicated. See the general statement on vitamin C.

BARRY LABORATORIES, INC.

Solution Sodium Ascorbate: 2 cc ampuls A sterile aqueous solution containing sodium ascorbate equivalent to 50 mg of ascorbic acid in each cubic centimeter.

ENDO PRODUCTS, INC.

Solution Sodium Ascorbate: 2 and 5 cc ampuls A sterile aqueous solution containing sodium ascorbate equivalent to 50 and 100 mg, respectively, of ascorbic acid in each cubic centimeter Stabilized with the equivalent of 0.08 per cent sulfurous acid

CARLO ERBA, INC.

Solution Sodium Ascorbate with Benzyl Alcohol 1%: 2 and 5 cc ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 50 and 100 mg, respectively, of ascorbic acid in each cubic centimeter.

GOLD LEAF PHARMACAL COMPANY, INC.

Solution Sodium Ascorbate: 2 and 5 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 50 and 100 mg, respectively, of ascorbic acid in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol and 0.1 per cent sodium bisulfite.

KREMERS-URBAN COMPANY

Solution Sodium Ascorbate: 2 cc ampuls A sterile aqueous solution containing sodium ascorbate equivalent to 50 mg. of ascorbic acid in each cubic centimeter.

LINCOLN LABORATORIES, INC.

Solution Sodium Ascorbate: 2 cc ampuls A sterile aqueous solution containing sodium ascorbate equivalent to 100 mg. of ascorbic acid in each cubic centimeter.

THE WM. S. MERRELL COMPANY

Solution Sodium Ascorbate: 2 cc ampuls A sterile aqueous solution containing sodium ascorbate equivalent to 50 mg of ascorbic acid in each cubic centimeter.

MEYER CHEMICAL COMPANY

Solution Sodium Ascorbate: 2 cc. ampuls. A solution containing sodium ascorbate equivalent to 50 mg of ascorbic acid in each cubic centimeter. Stabilized with 0.1 per cent sodium bisulfite and 0.1 per cent cysteine hydrochloride

2 and 5 cc ampuls. A solution containing sodium ascorbate equivalent to 0.1 Gm of ascorbic acid in each cubic centimeter Stabilized with 0.1 per cent cysteine hydrochloride and 0.1 per cent sodium bisulfite.

PARKE, DAVIS & COMPANY

Solution Sodium Ascorbate: 2 cc. ampuls. A solution containing sodium ascorbate equivalent to 50 mg. of ascorbic acid in each cubic centimeter. Preserved with 0.1 per cent sodium bisulfite.

WILLIAM H. RORER, INC.

Solution Sodium Ascorbate: 1 and 5 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 0.1 Gm. of ascorbic acid in each cubic centimeter. Preserved with 0.01 per cent aminoacetic acid.

SCHENLEY LABORATORIES, INC.

Solution Sodium Ascorbate: 5 cc. ampuls. A solution containing sodium ascorbate equivalent to 0.1 Gm. of ascorbic acid in each cubic centimeter.

STANDARD PHARMACEUTICAL COMPANY, INC.

Solution Sodium Ascorbate: 2 and 5 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 50 and 100 mg., respectively, of ascorbic acid in each cubic centimeter. Preserved with 0.4 per cent chlorobutanol and 0.2 per cent sodium bisulfite.

TESTAGAR & COMPANY

Solution Sodium Ascorbate: 2 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 50 mg. of ascorbic acid in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

5 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 100 mg. of ascorbic acid in each cubic centimeter. Preserved with 0.35 per cent chlorobutanol.

THE VITARINE COMPANY

Solution Sodium Ascorbate: 2 cc. ampuls. A solution containing sodium ascorbate equivalent to 50 mg. of ascorbic acid in each cubic centimeter.

5 and 10 cc. ampuls. A solution containing sodium ascorbate equivalent to 100 mg. of ascorbic acid in each cubic centimeter. All sizes preserved with 0.1 per cent sodium bisulfite and 0.5 per cent chlorobutanol.

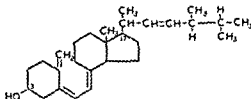
VITAMIN D

The term "vitamin D" is applied to two or more substances which have a function in the proper utilization of calcium and phosphorus. Two forms of naturally occurring vitamin D have been isolated. One of these, vitamin D₂, or calciferol, is obtained in pure crystalline form as one of the products of the ultraviolet irradiation of ergosterol; the other, vitamin D₃, can be prepared in the same manner from 7-dehydrocholesterol. Antirachitic activation of these compounds also can be accomplished by electronic bombardment. These two forms of vitamin D possess equal antirachitic

potency in man. They also tend to elevate the level of serum calcium, an effect which varies with the different substances and does not parallel the antirachitic effect.

The U.S.P. requires that the potency of vitamin D preparations be expressed, on the labeling, in U.S.P. units or the metric equivalent.

CALCIFEROL-U.S.P.—Disdol (WINTHROP-STEARNs).—Vitamin D₂—9,10-Ergostatetraene-(18, 10, 5, 6, 7, 8, 22, 23)-ol-3. The structural formula of vitamin D₂ may be represented as follows:



Physical Properties.—Calciferol occurs as white, odorless crystals. It is affected by air and by light. Calciferol is insoluble in water. It is soluble in alcohol, in chloroform, in ether and in fatty oils.

and phosphorus metabolism. Complications such as tuberculous deficiency or glandular malfunction may preclude normal response to vitamin D therapy. During acute infections, especially infections of the gastro-intestinal tract, vitamin D may prove ineffective because it is absorbed poorly. Animal experimentation has shown that correction of an inadequate intake of vitamin D results in the more economical utilization of calcium and phosphorus and also that the undesirable effects of improper ratios of calcium and phosphorus in the diet can be largely overcome by a normal intake of vitamin D. The application of these observations to man is not entirely apparent because adequate clinical evidence showing the availability of different forms of calcium and phosphorus is lacking, but it is certain that vitamin D has a favorable influence on the metabolism of calcium and phosphorus.

factor in the prevention or arrest of caries.

Direct exposure of the skin to ultraviolet rays from the sun or

the treatment of refractory rickets, that is, occasional cases of rickets which do not respond to treatment with the usual dosages or even much larger dosages of vitamin D. In some of these cases

the rickets is caused by a disturbance of the acid-base balance and has been treated successfully by administration of sodium bicarbonate or a sodium citrate-citric acid mixture. Massive doses of vitamin D also have proved effective in the control of other cases of rickets. The quantity of vitamin D needed may be so large that it borders on the dosages of vitamin D that are definitely toxic, and such treatment should not be undertaken without first exploring other possibilities or without careful observation for signs of toxicity. Some investigators believe it desirable to examine the urine daily for calcium casts, albumin and red blood cells while the maintenance dose is being established. Others believe less frequent examination is necessary. After the dose is established, weekly examination, using the Sulkowitch test for excessive excretion of calcium, is sufficient. The blood should be examined weekly or oftener to avoid a rise of calcium above 12 mg. per 100 cc if the dosage exceeds 20,000 units daily for the infant or 50,000 units for a child. If anorexia or nausea should appear, the child must be brought promptly to the attention of the physician and vitamin D administration should be discontinued. When the maintenance dose has been established, operative procedures to correct rachitic deformities may precipitate a temporary state of toxicity and the blood levels of calcium must be watched closely.

Vitamin D₂ (calciferol) and dihydrotachysterol, when administered in large doses, raise the level of serum calcium. This result is achieved in part by an increased absorption of calcium, and in part by mobilization of calcium from the bones. For this purpose these compounds may be given by mouth over considerable periods, provided the serum calcium does not rise above normal levels. An abnormally high level of calcium in the serum may have a serious or even fatal effect. There is no development of tolerance.

Because of its effect on the level of serum calcium, vitamin D is used in correcting hypocalcemia or parathyroid tetany. Vitamin D₂ and dihydrotachysterol have similar effects and are equally effective in the management of hypoparathyroidism. During their use frequent determinations of serum calcium are desirable. The Sulkowitch test is helpful and is so simple that it may be performed by the patient. Its routine use during treatment reduces the number of determinations of serum calcium that are necessary.

Large doses of vitamin D are of value in the treatment of lupus vulgaris. Clinical evidence does not warrant the use of massive doses of vitamin D in chronic arthritis, allergic disorders or psoriasis.

Dosage.—The vitamin D requirement apparently bears no relationship to the age of the individual. A daily intake of 400 units is believed to meet the ordinary requirements of all age groups. In treatment of the average case of rickets, 1,200 to 1,500 units daily appear to suffice. For massive dose therapy in refractory rickets, see the actions and uses statement.

Treatment of parathyroid insufficiency commonly is initiated with relatively large doses of the activated sterols, followed by smaller maintenance doses. The management of acute parathyroid

tetany may require 2 to 8 mg. of pure dihydrotachysterol which is approximately equivalent to 10 to 40 mg. or 400,000 to 1,600,000 international units of vitamin D. The amount of the substances necessary for daily maintenance varies greatly in individual cases but averages between 0.6 and 1 mg. of pure dihydrotachysterol or 3 to 5 mg. (120,000 to 200,000 I.U.) of vitamin D.

In recent years there have been reports of the successful use of large doses of vitamin D in the treatment of lupus vulgaris. The most effective dose of the vitamin in the treatment of this condition remains to be determined. Doses of the order of 100,000 to 200,000 units three times during the first week, twice during the second week and weekly thereafter have been used with apparent success. Precautions to avoid injury from excessive intakes of vitamin D should be observed as described in the actions and uses statement.

WINTHROP-STEARNs, INC.

Capsules Drisdol Concentrated Solution in Oil: 0.2 cc. Each capsule contains 1.25 mg. of calciferol and has a potency of 50,000 units of vitamin D (U.S.P.)

Solution Drisdol in Propylene Glycol: 5, 10 and 50 cc. bottles. Each cubic centimeter contains 0.25 mg. of calciferol and has a potency of 10,000 units of vitamin D (U.S.P.) per gram. The propylene glycol used in the preparation of this product complies with the standards for propylene glycol-N.N.R.

Capsules Drisdol with Vitamin A: 5,000 U.S.P. units of vitamin A and 1,000 U.S.P. units of vitamin D in corn oil.

Solution Drisdol with Vitamin A (Water Dispersible): 10 and 50 cc. bottles. 50,000 U.S.P. units of vitamin A and 10,000 U.S.P. units of vitamin D per gram in sesame oil.

U. S. trademark 333,661.

VITAMIN E

In 1925 it was demonstrated conclusively that vitamin E must be included in the diet of the rat to ensure successful reproduction. There are at least three naturally occurring compounds which have vitamin E activity: alpha, beta and gamma tocopherol. The role of vitamin E in human physiology has not been determined. There seems to be agreement that the vitamin is of no value in the treatment of sterility and of dubious value in the treatment of habitual abortion.

It has been claimed that vitamin E is of value in the treatment of many common, serious diseases. Carefully controlled experiments have not substantiated these claims.

VITAMIN K

Hypoprothrombinemia results from an inadequate supply of vitamin K to the liver as occurs when the vitamin is absorbed

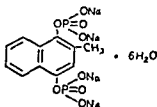
poorly, from hepatic disease that incapacitates the liver for prothrombin formation or from antagonism to prothrombin formation as produced by certain anticoagulants. In general this condition responds promptly to proper administration of the vitamin.

Investigations have shown that there are at least two naturally occurring vitamin K's; they are referred to as vitamin K₁ (C₃₁H₄₆O₂) and Vitamin K₂ (C₄₁H₅₆O₂).

There are also a number of synthetic naphthoquinone derivatives, referred to as vitamin K analogues, that produce a wide range of vitamin K activity. Some of them are water-soluble.

The *U.S.P.* requires that the potency of vitamin K preparations be expressed in milligrams on labels.

MENADIOL SODIUM DIPHOSPHATE-U.S.P.—*Synkayvite Sodium Diphosphate* (HOFFMANN-LA ROCHE)—The hexahydrate of the tetrasodium salt of 2-methyl-1,4-naphthafenediol diphosphate—"Menadiol Sodium Diphosphate contains not less than 97.5 per cent of C₁₁H₈Na₄O₈P₂, calculated on the anhydrous basis." *U.S.P.* The structural formula of menadiol sodium diphosphate may be represented as follows



Physical Properties.—Menadiol sodium diphosphate is a white or pink to light brown hygroscopic powder with a characteristic odor. It is very soluble in water and insoluble in alcohol and ether. The pH of a 1 per cent solution is 7.8 to 8.5.

Actions and Uses.—Menadiol sodium diphosphate, a dihydro derivative of menadione, has the same actions and uses as other analogues of vitamin K. Therefore, it is useful in the prevention and treatment of hemorrhagic disorders associated with hypoprothrombinemia caused by a deficiency of vitamin K, overdosage of systemic anticoagulants such as bishydroxycoumarin, or secondary to the administration of large doses or the prolonged use of salicylates, quinine, sulfonamides, arsenicals and barbiturates. It also is indicated in physiologic hypoprothrombinemia of the newborn as well as in prothrombin deficiency caused by gastro-intestinal disorders that interfere with the absorption of the vitamin, including deficiency of intestinal bile that is essential for the absorption of natural and fat soluble forms of vitamin K. Menadiol sodium diphosphate is water soluble and, therefore, absorbed following oral administration without bile salts. It also is effective by parenteral administration.

Dosage.—Menadiol sodium diphosphate is administered orally and by injection subcutaneously, intramuscularly or intravenously. On the basis of molecular weights, the dosage should be at least

three times that of menadione to provide a theoretically equivalent amount of vitamin K activity. The calculated ratio is 3.1 mg of menadiol sodium diphosphate to 1 mg of menadione. For the management of prothrombin deficient hemorrhagic states, the average dose for adults should range from 3 to 6 mg daily and may be administered orally or parenterally as the situation requires. Larger doses may be given if necessary. As an antidote for bishydroxycoumarin overdosage, a dose of 75 mg intramuscularly, repeated as often as necessary, is recommended. For the prevention of hemorrhage associated with prothrombin deficiency caused by salicylates after tonsillectomy, a total daily dosage of 10 to 25 mg (administered in three divided doses) is recommended. For the prevention of hemorrhagic disease of the newborn, either 6 to 12 mg. is administered parenterally to the mother during labor, or 3 mg. is given to the infant immediately after delivery.

HOFFMAN-LA ROCHE, INC.

Solution Synkayvite Sodium Diphosphate. 1 cc ampuls. An isotonic solution containing 5 or 10 mg of menadiol sodium diphosphate in each cubic centimeter.

2 cc ampuls. An isotonic solution containing 37.5 mg of menadiol sodium diphosphate in each cubic centimeter. Stabilized with sodium metabisulfite and preserved with 0.45 per cent phenol.

Tablets Synkayvite Sodium Diphosphate: 5 mg

U S patent 2,354,132 U S trademark 393,117

MENADIONE-U.S.P.—Menaphthene—Menaphthone—2-Methyl-1,4-naphthoquinone.—“Menadione, dried over sulfuric acid for 4 hours, contains not less than 98.5 per cent of $C_{11}H_8O_2$.” *U.S.P.* The structural formula of menadione may be represented as follows:



Physical Properties.—Menadione is a bright yellow, crystalline powder. It is nearly odorless and is affected by sunlight. It is practically insoluble in water. One gram dissolves in about 60 cc of alcohol. It is soluble in vegetable oils.

Actions and Uses.—Menadione is a synthetic naphthoquinone derivative having the physiologic properties of vitamin K.

Menadione is highly effective against the hemorrhagic diathesis of obstructive jaundice and biliary fistula. Because menadione is fat-soluble, it is not absorbed when the flow of bile is obstructed or otherwise diverted from the intestine, thus depriving the liver of a necessary constituent for the formation of prothrombin and resulting in a prothrombin deficiency. To overcome prothrombin

deficiency secondary to bile obstruction or biliary fistula, menadione either must be given parenterally or orally with bile salts, unless a water-soluble preparation is used.

The hemorrhagic state associated with primary hepatic disease is controlled in part by menadione and its analogues. The efficiency of this treatment is limited because in the formation of prothrombin the diseased liver can utilize the administered vitamin only to a limited extent.

The hemorrhagic states that exist in connection with certain intestinal disorders, such as ulcerative colitis, sprue, celiac disease and certain postoperative states characterized either by a loss of continuity of the intestinal tract or by a disturbance of its absorptive surface, also are favorably affected by menadione.

Menadione also is indicated when orally administered anti-infective agents, such as sulfonamides or antibiotics, so inhibit bacterial growth that endogenous formation of vitamin K is decreased critically. Furthermore, it is effective against the prothrombin depressing action of other agents such as salicylates.

In the treatment of physiologic hypoprothrombinemia of the newborn, which exists during the first week of life, and in the prevention of the consequent hemorrhage, the vitamin and its analogues usually are beneficial. As little as 0.5 to 2 mg. of the vitamin or the naphthoquinones, when administered parenterally to a woman during labor, ensure that the newborn infant will have a normal amount of prothrombin in the circulating blood. The same doses given parenterally to the newborn infant also produce this effect.

The administration of menadione also is effective in the extremely rare cases of primary dietary deficiency of vitamin K.

Dosage.—The therapeutic dosage is 1 to 2 mg. daily or as prescribed by the physician. In prothrombin deficiency caused by bile obstruction, bile salts should be administered with menadione.

The Council on Pharmacy and Chemistry has recommended that the marketing of dosage sizes of menadione should be limited to 1 or 2 mg. tablets or capsules and concentrations of 1 or 2 mg. per cubic centimeter for solutions.

"Caution.—*Menadione powder is irritating to the respiratory tract and to the skin, and an alcoholic solution has vesicant properties.*" U.S.P.

R. E. DWIGHT & COMPANY

Capsules Menadione: 2 mg.

ENDO PRODUCTS, INC.

Solution Menadione in Oil: 2 cc. ampuls. A solution in corn oil containing 1 mg. of menadione in each cubic centimeter.

Tablets Menadione: 1 and 2 mg.

GOLD LEAF PHARMACAL COMPANY, INC.

Tablets Menadione: 2 mg.

LINCOLN LABORATORIES, INC.

Solution Menadione in Oil with Benzyl Alcohol 2%: 15 cc vials
A solution in sesame oil containing 2 mg of menadione in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

E. S. MILLER LABORATORIES, INC.

Solution Menadione in Oil: 1 cc ampuls A solution containing 1 mg of menadione with 2 per cent benzocaine in each cubic centimeter. Preserved with 0.5 per cent cresol

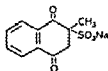
Tablets Menadione: 1 mg.

U. S. VITAMIN CORPORATION

Capsules Menadione: 1 mg. and 2 mg

Solution Menadione in Oil: 1 cc ampuls A solution in corn oil containing 1 mg. of menadione in each cubic centimeter

MENADIONE SODIUM BISULFITE-U.S.P.—Hykinone (Abbott) —
"Menadione Sodium Bisulfite contains not less than 94 per cent of $C_{11}H_8O_2NaHSO_3$, calculated on the anhydrous basis." *U.S.P.* It may be prepared by the interaction of menadione and sodium bisulfite to form the addition product. The structural formula of menadione sodium bisulfite may be represented as follows



Physical Properties.—Menadione sodium bisulfite occurs as a white, crystalline, odorless hygroscopic powder. One gram of menadione sodium bisulfite dissolves in about 2 cc of water. It is slightly soluble in alcohol and is almost insoluble in ether and in benzene.

Actions and Uses.—Menadione sodium bisulfite is used for the same conditions as is menadione, which possesses the physiologic properties of vitamin K. Unlike menadione it is soluble in water, and stable aqueous solutions may be prepared. Since this material is water soluble, it is effective administered orally without the use of bile salts in conditions where the flow of bile is obstructed.

Dosage.—It may be administered subcutaneously, intramuscularly or intravenously, the average daily dose being 0.5 to 2 mg. During administration of the drug the prothrombin level of the blood should be followed, especially when there appears to be need of an additional dose during a 24-hour period. In patients under treatment with bishydroxycoumarin, if prothrombin activity drops to low 15 per cent or signs of bleeding appear, 50 to 100 mg of menadione sodium bisulfite are given by slow intravenous injection.

ABBOTT LABORATORIES

Solution Hykinone: 10 cc. ampuls An isotonic sodium chloride

solution containing 7.2 mg. of menadione sodium bisulfite in each cubic centimeter. Stabilized with 0.36 per cent sodium bisulfite.

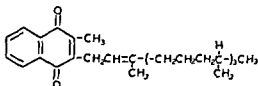
U. S. patent 2,367,302. U. S. trademark 514,207.

THE Wm. S. MERRELL COMPANY

Solution Menadione Sodium Bisulfite: 1 cc. ampuls. A solution containing 3.84 mg of menadione sodium bisulfite in each cubic centimeter. Stabilized with 0.14 per cent sodium bisulfite.

U. S. patent 2,331,808.

PHYTONADIONE-U.S.P.—*Mephyton* (SHARP & DOHME)—2-Methyl-3-phytyl-1,4-naphthoquinone—Vitamin K₁.—The structural formula of phytonadione may be represented as follows:



Physical Properties.—Phytonadione is a yellow, very viscous, nearly odorless liquid. It is stable in air but decomposes in sunlight. It is soluble in alcohol, benzene, chloroform, ether and vegetable oils and insoluble in water. A solution of 1 part phytonadione and 20 parts alcohol is neutral to litmus.

Actions and Uses.—Phytonadione has a more prompt, more potent and more prolonged effect than the vitamin K analogues.

Its reliability in treating undue hypoprothrombinemia from anticoagulant therapy is of particular importance. Phytonadione can be depended on to reverse anticoagulant induced hypoprothrombinemia to safe levels whether bleeding is only potential or actually has occurred. An adequate intravenous dose of the emulsion of the vitamin usually will stop bleeding in 3 to 4 hours and produce a normal prothrombin level in 12 to 14 hours.

See the monograph on menadione for other uses.

Dosage.—Phytonadione is available in an emulsion designed specifically for intravenous use.

For the treatment of undue anticoagulant-induced hypoprothrombinemia, 50 to 100 mg. is recommended. Dosage for hypoprothrombinemia from other causes varies widely depending on the nature and severity of the condition. In obstructive jaundice or biliary fistula as little as 2 mg. daily may suffice, yet as much as 20 mg. or more a day may be required, in gastro-intestinal disorders interfering with absorption of the vitamin, 5 to 15 mg. or more daily may be needed, in hepatic disease, 50 mg. three times a week has been reported useful; for hemorrhagic disease of the newborn, 0.5 to 2 mg. is considered adequate for prophylaxis—for treatment, up to 10 mg. may be used.

The emulsion of phytonadione should be given not faster than 10 mg. per minute. Administration is facilitated by mixture with a suitable diluent such as water for injection-U.S.P. or sterile

isotonic sodium chloride for parenteral use-U.S.P.; 5 to 7 cc. or more of the diluent is used to each cubic centimeter of the emulsion.

rol anticoagulant-induced embolism. It is emulsified so that the patient is protected from the risks of intravascular clot-therapy. Therefore, properly so that the prothrom-

bin may be balanced properly between levels protecting the patient from intravascular clotting on the one hand and pathologic bleeding on the other. If subsequent anticoagulant therapy is needed and if the patient has been rendered temporarily resistant to prothrombin depressing agents, heparin may be used.

SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Emulsion Mephyton: 1 cc. ampuls. An emulsion containing 50 mg. of phytonadione in each cubic centimeter.

U. S. trademark 582,261.

MIXED VITAMINS

Preparations of Vitamins A and D

Concentrates from fish liver oils and concentrates of vitamin D are used in the manufacture of a variety of vitamin A and D preparations that are used therapeutically and prophylactically. For actions, uses and dosage of vitamins A and D, see monographs on oleovitamin A and calciferol.

BURBOT LIVER OIL.—The oil extracted from the livers of the Burbot (*Lota maculosa*), family Gadidae. It has a potency of not less than 4,880 U.S.P. units of vitamin A per gram and of not less than 640 U.S.P. units of vitamin D per gram.

Physical Properties.—Burbot liver oil is a pale, yellow, oily liquid. It has a slightly fishy, but not rancid, odor and a fishy taste. It is soluble in benzene, carbon disulfide, chloroform, ether and ethyl acetate and is slightly soluble in alcohol.

Actions, Uses and Dosage.—See the monographs on oleovitamin A and calciferol.

ROWELL LABORATORIES, INC.

Burbot Liver Oil: 60 and 240 cc. bottles.

Capsules Burbot Liver Oil: 0.5 cc. adjusted to have a potency of not less than 2,215 U.S.P. units of vitamin A and 315 U.S.P. units of vitamin D per capsule.

CONCENTRATED OLEOVITAMIN A AND D.—Concentrated oleovitamin A and D is either fish liver oil, or fish liver oil diluted with an edible vegetable oil, or a solution of Vitamin A and D concentrates in fish liver oil or in an edible vegetable oil. The vitamin A is obtained from natural (animal) sources or from

synthetic vitamin A or its fatty-acid esters and the vitamin D may be from natural (animal) sources or may be synthetic oleovitamin D. Concentrated oleovitamin A and D contains in each gram not less than 50,000 and not more than 65,000 U.S.P. units of vitamin A, and not less than 10,000 and not more than 13,000 U.S.P. units of vitamin D.

Physical Properties.—Concentrated oleovitamin A and D is a thin, oily liquid which may have a fishy, but not a rancid, odor and taste.

Actions, Uses and Dosage.—See the monographs on oleovitamin A and calciferol.

McKesson & Robbins, Inc.

Concentrated Oleo Vitamins A and D: 6 cc. vials. A concentrate of vitamins A and D prepared from cod liver oil, the concentrate containing not less than 60,000 U.S.P. units of vitamin A and not less than 10,000 U.S.P. units of vitamin D per gram.

WALKER LABORATORIES, INC.

Drops Concentrated Oleo Vitamin A and D: Each gram contains not less than 62,500 U.S.P. units of vitamin A and not less than 10,000 U.S.P. units of vitamin D. Natural esters of vitamin A (distilled from fish liver and vegetable oils) plus activated ergosterol in refined corn oil. Flavored with cinnamon.

PERCOMORPH LIVER OIL.—*Oleum Percomorphum.*—A blend of the fixed oils obtained from the fresh livers of the percomorph fishes, principally *Xiphias gladius*, *Pneumatophorus diego*, *Thunnus thynnus* and *Stereolepis gigas*—sometimes also *Neothunnus macropterus*, *Katsuwonus pelamis*, *Sarda chilensis*, *Germo alalunga*, *Thunnus orientalis*, *Scomber scombrus*, *Seriola dorsalis*, *Lutianus campechanus*, *Epinephelus morio*, *Roccus lineatus*, *Cynoscion nobilis*, *Eriscion macdonaldi*, *Epinephelus analogus*, *Stereolepis ishinagi* and *Sphyræna argentea*. Percomorph liver oil may be blended with 50 per cent of other fish liver oils. It has a potency of not less than 60,000 U.S.P. units of vitamin A per gram and of not less than 8,500 U.S.P. units of vitamin D per gram.

Physical Properties.—The material is a yellow to brownish-yellow, oily liquid with a fishy taste and odor. It is soluble in benzene, carbon disulfide, chloroform, ether and ethyl acetate and slightly soluble in alcohol.

Actions, Uses and Dosage.—Same as those of cod liver oil. See the monographs on oleovitamin A and calciferol.

AFRICAN PHARMACEUTICAL COMPANY, INC.

Oleum Percomorphum, Codanol Brand, with Other Fish Liver Oils and Vitamin D: 10 and 50 cc. A source of vitamin A and D in which not less than 50 per cent of the vitamin content is derived from the live fish. Each gram contains not less than 60,000 U.S.P. units of vitamin A and 8,500 U.S.P. units of vitamin D.

MEAD JOHNSON & COMPANY

Capsules Oleum Percomorphum with Other Fish Liver Oils and Viosterol: Each capsule contains 83 mg of percomorph with other fish liver oils and viosterol and supplies a potency of 5,000 U.S.P. units of vitamin A and 700 U.S.P. units of vitamin D

Oleum Percomorphum with Other Fish Liver Oils and Viosterol: 10 and 50 cc. bottles. A blend of percomorph liver oil with other fish liver oils and viosterol which contains not less than 60,000 U.S.P. units of vitamin A and 8,500 U.S.P. units of vitamin D in each gram

Other Mixed Vitamin Preparations

HEXAVITAMIN-N.F.—"Hexavitamin Capsules [and Tablets] contain in each capsule (or tablet) not less than 5,000 U.S.P. Units of Vitamin A from natural (animal) sources or from synthetic Vitamin A or its fatty-acid esters, 400 U.S.P. Units of Vitamin D from natural (animal) sources or as calciferol or activated 7-dehydrocholesterol, 75 mg of ascorbic acid, 2 mg of thiamine hydrochloride, 3 mg. of riboflavin and 20 mg of nicotinamide" *N.F.*

Actions, Uses and Dosage.—For prophylaxis and treatment of conditions arising from deficiency of vitamin A, vitamin D, ascorbic acid, thiamine, riboflavin and nicotinic acid, see the monographs on the various vitamins concerned.

THE WM. S. MERRELL COMPANY

Tablets Hexavitamin: Each tablet contains 5,000 U.S.P. units of vitamin A, 400 U.S.P. units of vitamin D, 2 mg of thiamine hydrochloride, 3 mg. of riboflavin, 75 mg. of ascorbic acid and 20 mg. of nicotinamide.

WALKER LABORATORIES, INC.

Capsules Hexavitamin: Each capsule contains 5,000 U.S.P. units of vitamin A, 400 U.S.P. units of vitamin D, 2 mg of thiamine, 3 mg. of riboflavin, 75 mg. of ascorbic acid and 20 mg of niacinamide

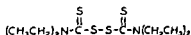
TRIASYN B (See under mixed vitamin B components)

Miscellaneous Therapeutic Agents

A number of drugs of considerable value do not fall under any of the major chapter headings that group preparations of similar or related action or use.

AGENTS FOR TREATMENT OF ALCOHOLISM

DISULFIRAM.—*Antabuse* (AYERST) —Bis(diethylthiocarbamyl) disulfide—The structural formula of disulfiram may be represented as follows.



Physical Properties.—Disulfiram is a white to light gray, odorless and almost tasteless powder. The amounts that dissolve in the following solvents to form 100 cc of solution are: 3.82 Gm. in alcohol, 7.14 Gm. in ether and 0.02 Gm. in water.

Actions and Uses.—Disulfiram, an antioxidant, apparently interferes with the normal metabolic degradation of alcohol in the body, resulting in an increased acetaldehyde concentration in the blood. Perfusion experiments suggest that it acts principally on the enzyme systems of the liver. It does not affect the rate of elimination of alcohol from the body. Regular oral administration of disulfiram, if followed by the ingestion of small amounts of alcohol, causes a highly unpleasant reaction, the severity of which can be correlated with the blood levels of acetaldehyde and ethyl

alcohol. Prolonged administration of disulfiram with alcoholic beverages requires the supervision of the patient and is expected if

drinking is resumed, and relatives should be instructed concerning the danger of secret administration of the drug. Personality changes have been reported as a consequence of the sudden withdrawal of alcohol, particularly when disulfiram was administered against the wishes of the patient. A complete history, preferably in the presence of a relative, and a thorough physical examination are essential.

The effectiveness of disulfiram as an aid in overcoming the drinking habit depends upon the demonstration of the unpleasant effects produced following ingestion of even a small amount of alcohol. This is accomplished by administering a trial dose of 15 cc of 100 proof whisky followed immediately by small amounts of other alcoholic beverages, if such intoxicants might be used by the patient, and demonstrating the reaction produced on others or the patient himself following drug therapy.

Because disulfiram at the dosage now advised is absorbed slowly by the intestinal tract, therapy must be maintained preferably for about 3 weeks before the drug can be counted on to produce a satisfactory reaction to the ingestion of alcohol. Since it is excreted slowly from the intestinal tract, symptoms will follow the ingestion of alcohol taken as long as a week after administration of a single large dose of the drug, indicating that it has a prolonged effect.

The reaction produced by disulfiram and alcohol is characterized by flushing, palpitations, dyspnea, hyperventilation, acceleration of pulse rate, anoxia, fall in blood pressure, nausea, vomiting and, occasionally, collapse. Drowsiness usually follows with complete recovery after sleep. The severity of the reaction varies with each person and with the amounts of disulfiram and alcohol taken. All types of alcoholic beverages will produce a reaction in patients receiving disulfiram when the blood alcohol concentration is increased to as little as 5 to 10 mg per 100 cc. Fully developed symptoms are observed at a level of 50 mg per 100 cc, unconsciousness occurs at levels of 125 to 150 mg per 100 cc. Heavy drinkers may tolerate large amounts, but tolerance to alcohol tends to disappear with continued administration of the drug. Tolerance to disulfiram does not develop, nor is it habit forming.

Although disulfiram is of low toxicity when used in the recommended dosage, extreme caution is necessary during its use because severe and alarming reactions to alcohol have been reported in patients on disulfiram. These include cardiovascular complications involving unusual fall in blood pressure, cardiac arrhythmia, electrocardiographic evidence of myocardial ischemia and even myocardial infarction. Such reactions have resulted usually from excessive trial doses of alcohol or surreptitious drinking during initial stages of treatment, therefore, careful and continuous medical supervision is important.

Some patients on disulfiram therapy complain of mild drowsiness, fatigability, impotence, headache or peripheral neuritis, but such symptoms tend to subside with continuation of the drug at a reduced dosage. Because of neurologic changes in animals and toxic psychoses observed in human beings receiving large doses, it is essential to limit the daily dose of the drug. Rare instances of skin eruption, which usually can be controlled by concomitant administration of one of the antihistamine drugs, have been reported.

Although there are no known absolute contraindications, the alcohol test usually is omitted when disulfiram is to be given to patients over 50 years of age or when used in the presence of diabetes mellitus, goiter, epilepsy, psychosis, cirrhosis of the liver

or chronic or acute nephritis. The alcohol test must not be given to patients with myocardial failure, coronary disease or pregnancy. Caution should be exercised when addiction to narcotics is superimposed on alcoholism.

When sedation is required, strict supervision is essential to prevent habituation to barbiturates as a substitute for alcoholism. Disulfiram should not be used in patients recently treated with paraldehyde, and paraldehyde should not be given to patients receiving disulfiram. Disulfiram itself may produce a calming effect conducive to sleep that may lessen the need for sedatives.

Dosage.—Disulfiram is administered orally. The patient should not consume any alcoholic beverage for at least 12 hours before the drug is administered. It is particularly important to refrain from treatment when intoxication is present. The initial dosage should be limited to a maximum of 0.5 Gm. daily for the first 2 or 3 weeks, and subsequent maintenance dosage should not exceed that amount. The usual maintenance dose is about 0.25 Gm., ranging from 0.125 to 0.5 Gm. daily. The dosage should be sufficient for the patient to experience flushing of the face after taking 15 cc. of 100 proof whisky or its equivalent (approximately 7.5 Gm. of 95 per cent alcohol). Uninterrupted administration of the drug should be continued until the patient is recovered socially and a basis for permanent self-control is established. Since therapy depends on the individual patient, it may need to be continued for a period lasting from several months to years. When indicated, a test dose of alcohol is given after the first 2 or 3 weeks of therapy. This should be supervised carefully by the physician, in a hospital if necessary, and a supply of oxygen should be readily available for administration in the event of a severe reaction.

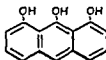
AYERST LABORATORIES, INC.

Tablets Antabuse: 0.5 Gm

U. S. patent 2,567,814

ANTHRACENE DERIVATIVES

ANTHRALIN-N.F.—1,8,9-Anthratriol.—“Anthralin, dried over sulfuric acid for 4 hours, contains not less than 95 per cent of $C_{14}H_{10}O_3$.” *N.F.* The structural formula of anthralin may be represented as follows.



Physical Properties.—Anthralin occurs as an odorless, tasteless, crystalline, yellowish brown powder. When suspended in water and filtered, the filtrate is neutral to litmus paper. It is soluble in chloroform, in acetone and in benzene. It is soluble in solutions of alkali hydroxides and slightly soluble in alcohol, in ether and in glacial acetic acid. It is insoluble in water.

Actions and Uses.—Anthralin is recommended as a substitute for chrysarobin in the treatment of psoriasis because it has less tendency to produce conjunctivitis when used about the face and scalp and less tendency to cause dermatitis or discoloration of the skin. The preparation also has been recommended in the treatment of chronic dermatomycosis and for stimulating action in chronic dermatoses.

Dosage.—Anthralin is employed in concentrations of 0.1 per cent to 1 per cent in ointments or creams. It is always well to begin with lower concentrations because anthralin tends to irritate the skin.

ABBOTT LABORATORIES

Ointment Anthralin. 0.1, 0.25, 0.5 or 1 per cent anthralin in a petrolatum base.

ANTIDOTES FOR HEAVY METAL POISONING

DIMERCAPROL—U.S.P.—BAL (HYNSON, WESTCOTT & DUNNING) — 2,3-Dimercaptopropanol — “Dimercaprol contains not less than 99 per cent of $C_3H_6OS_2$ ” *U.S.P.* The structural formula of dimercaprol may be represented as follows



Physical Properties.—Dimercaprol is a colorless or almost colorless liquid with an offensive, mercaptanlike odor. It is soluble in water (1 in 13), soluble in alcohol, in methanol and in benzyl benzoate.

Actions and Uses.—Dimercaprol in oil is indicated in the treatment of arsenic, gold and mercury poisoning. Results in the treatment of other heavy metal poisoning such as antimony and bismuth have been inconclusive and results in lead poisoning have been disappointing in animal experiments but less certainly so in man.

Dimercaprol, by virtue of being a dithiol, competes with physiologically essential cellular -SH groups for arsenic, mercury and gold, thus preventing combination of the heavy metal with these groups. The stable combination of dimercaprol and heavy metal is excreted rapidly and the body thus freed quickly of the toxic agent.

Dimercaprol is particularly useful in the treatment of hemorrhagic encephalitis due to massive arsenotherapy, arsenical or gold dermatitis and possibly postarsenical jaundice. It is not helpful in homologous serum jaundice or infectious hepatitis. It is useful as an adjunct in the treatment of agranulocytosis due to arsenic, but other measures, principally massive doses of penicillin, also must be employed.

While dimercaprol in oil is indicated in the treatment of mercury

poisoning, it must be remembered that mercury causes rapid and extensive tissue damage, particularly to the kidneys, which cannot be corrected by the administration of dimercaprol. The use of dimercaprol in oil in the treatment of mercury poisoning still is in the experimental stage and definite recommendations cannot be made.

The toxicity of dimercaprol is less in patients suffering from arsenic, gold or mercury poisoning, but doses of 300 mg. (5 mg per kilogram of body weight) may produce nausea, vomiting and headache, a burning sensation of the lips, mouth, throat and eyes, generalized muscular aches with burning and tingling of the extremities and a sense of constriction in the chest. The symptoms usually subside in 30 to 90 minutes.

Dosage.—In the treatment of arsenic or gold poisoning, 3 mg. of dimercaprol per kilogram of body weight (as a 10 per cent solution in oil) should be administered by intramuscular injection every 4 hours for the first 2 days; four injections should be given on the third day, and two injections daily thereafter for 10 days or until complete recovery. In milder cases, the dose may be reduced to 2.5 mg. per kilogram of body weight.

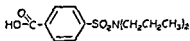
HYNSON, WESTCOTT & DUNNING, INC.

Solution BAL in Oil. 4.5 cc ampuls. A solution in peanut oil containing 10 per cent dimercaprol and 20 per cent benzyl benzoate.

BLOCKING AGENTS AT THE RENAL TUBULES

A number of drugs, including penicillin, may be secreted actively by the renal tubules, and agents have been sought that would block this action and so maintain the blood levels of the drugs more easily. Carinamide and, more recently, probenecid have been used for this purpose. Another recent application of probenecid is in gout, where the excretion of urates is promoted more satisfactorily than with the older salicylates or cinchophens by blocking the urate absorption carrier system of the tubule.

PROBENECID—Benemid (SHARP & DOHME).—*p*-(Dipropylsulfamyl)benzoic acid.—The structural formula of probenecid may be represented as follows:



Physical Properties.—Probenecid is a white, odorless, crystalline powder which melts between 198 and 200°. It is soluble in acetone, chloroform, carbon tetrachloride, and in bicarbonate and insoluble

in water. It is a weakly acidic ion, interfering with the renal tubular excretion of certain organic compounds such as penicillin, amino-salicylic acid, and phenolsulfonphthalein. It also acts as a urate

eliminant by depressing the renal tubular resorption of urate, thus increasing the urinary excretion and reducing the serum level of uric acid. Probenecid, therefore, is useful as an adjuvant to intensive therapy with penicillin or aminosalicylic acid to increase and prolong the plasma concentrations of these anti-infective agents, and as an agent to promote the elimination of uric acid in the interval treatment of gout and the treatment of chronic gouty arthritis. Its suppression of the renal clearance of phenol-sulfonphthalein (phenol red) is of significance in the application of that kidney excretion test as a clinical guide to the effectiveness of probenecid. Analytic methods also are available for determination of probenecid metabolites in the body fluids.

Probenecid plasma levels of 2 to 10 mg. per 100 cc. have been correlated with effective plasma levels of penicillin and of aminosalicylic acid. Probenecid is capable of producing a twofold to tenfold increase in plasma levels of penicillin and a 15 to 50 per cent increase of plasma levels of aminosalicylic acid. Therefore, it can be used to increase the effectiveness of orally administered penicillin and to reduce the dose required for adequate therapy by either the oral or intramuscular route. It may enhance the effectiveness of aminosalicylic acid in tuberculosis by increasing its plasma level above the usual limits attainable with oral administration without causing gastric distress.

The reabsorption of glucose, arginine, urea or creatinine from the urine is not influenced by probenecid, nor does it affect the excretion of streptomycin, chloramphenicol, chlortetracycline or oxytetracycline. It raises the plasma concentration of the presumably biologically inactive conjugated sulfonamides, but the insignificant increase it produces in the free sulfonamide level is considered to be inconsequential therapeutically. However, when sulfonamides are administered in conjunction with probenecid, it is suggested that an occasional sulfonamide plasma determination be made in the same manner that is recommended during any sulfonamide therapy.

Probenecid may precipitate an acute attack of gouty arthritis when used as a urate eliminant in chronic gout. Also, by retarding the urinary reabsorption of urates, it is possible that probenecid may favor the formation of uric acid stones from urates that would tend to crystallize in an acid urine. Colchicine should be administered without discontinuing probenecid to manage acute attacks of gout, and the precipitation of urates can be minimized by maintaining the urine alkaline to litmus. *For the therapy of gout, salicylates should not be administered in conjunction with probenecid because the therapeutic actions of the two drugs are antagonistic.* Probenecid has no analgesic action and is of no value in the treatment of acute gout. Serious anaphylactoid reactions are extremely rare.

Probenecid is absorbed rapidly into the blood stream following oral administration and is eliminated promptly by glomerular filtration. However, its reabsorption by the renal tubules is so great that the renal clearance cannot be estimated because little or none appears in the urine. It is metabolized slowly and its

metabolic products are only slowly excreted in the urine. Following a single oral dose, a determinable and functionally useful plasma concentration persists in the dog for longer than 44 hours. A high therapeutic index has been demonstrated in a variety of laboratory animals. Although probenecid is well tolerated in man and is of low toxicity at useful dosages, occasionally patients may experience nausea. This may be overcome by reduction of the daily dosage. Rarely, sensitivity may be manifested by the appearance of a skin rash, but such reactions have been observed much less frequently following therapy with probenecid than following the administration of antibiotics. If a rash appears, therapy with probenecid should be discontinued until the cause of the reaction

discontinued.

Probenecid obviously will serve no useful purpose in elevating the plasma concentration of penicillin in the presence of known renal impairment. When there is glomerular involvement, its rapid accumulation in the plasma may cause nausea or other toxic symptoms. Even in the presence of renal damage, probenecid does not exhibit toxic action on the kidney.

Dosage.—Probenecid is administered orally. As an adjuvant to penicillin therapy of severe infections such as subacute bacterial endocarditis and staphylococcal osteomyelitis, the total daily dosage in absence of renal disease is 2 Gm given in four divided doses. The dose should be reduced for older persons in whom renal impairment is more likely to be present. When impairment is sufficient to retard the tubular excretion of penicillin, probenecid is not necessary and may not be tolerated. When used in conjunction with penicillin therapy of children, the recommended initial dosage is 25 mg per kilogram of body weight, which should be followed by 10 mg per kilogram every 6 hours for maintenance therapy. For children weighing more than 50 kilograms, the adult dose is adequate. The dosage of probenecid when used with aminosalicilic acid is similar and subject to the same precautions. The phenolsulfonphthalein (phenol red) excretion test employed by the intravenous (15-minute) method can be used as an index of effective plasma concentrations of probenecid. The renal clearance of phenol red is reduced to approximately one-fifth of the normal rate with adequate dosage of probenecid.

As a urate eliminant in chronic gout, a daily single dose of 0.5 Gm is recommended for 1 week, then increased to 1 Gm daily in two divided doses. Usually, this is adequate as a maintenance dose because renal impairment is common in patients with gout. However, for some patients it may be desirable to increase the total daily dosage to 2 Gm, given in four divided doses, to obtain optimal excretion of uric acid. The urine can be maintained

SHARP & DOHME, DIVISION OF MERCK & CO., INC.

Tablets Benemid: 0.5 Gm.

U. S. patent 2,608,507. U. S. trademarks 547,248 and 567,175.

BURN DRESSINGS

ZINCASATE BURN DRESSING.—Zinc Burn Dressing (HYNSON, WESTCOTT & DUNNING)—Zincasate burn dressing consists of zincasate gel, a partially hydrolyzed casein gel, and zincasate gauze, a zinc acetate impregnated gauze.

Physical Properties.—Zincasate gel is a pinkish-tan, viscous liquid. The gel has a pH of 6.5 to 7.0. It is coagulated readily by zinc acetate.

Actions and Uses.—Zincasate, a combination of partially hydrolyzed casein gel and zinc acetate impregnated gauze to be applied separately, is used as a dressing for the local treatment of burns by the closed pressure bandage technic. The gel, first applied over the injured area, is converted promptly into an insoluble coagulum at the point of contact with the zinc acetate impregnated gauze to form an adherent, protective, semipermeable membrane that permits the evaporation of water while reducing the loss of transudates. The gel will set eventually without the aid of zinc acetate gauze, so that the layer next to the wound is not coagulated immediately. The gauze, through its union with the adherent gel, provides some pressure and a surface to which an elastic bandage can be applied to increase pressure where this is feasible. The combined use of these materials should follow the same general principle and aseptic technic applicable to the use of petrolatum and plain gauze. The use of a coagulable protein and zinc acetate gauze has the slight advantage of convenience of application, avoidance of maceration, less need for redressing and production of a pliable protective film permitting easier movement and transport of the patient.

Dosage.—Zincasate gel and gauze dressing are applied after removal of obvious dirt or necrotic tissue, with sterile technic, but without surgical débridement. The casein gel should be applied to superficial as well as to more deeply injured areas to a thickness of not less than $\frac{1}{8}$ in. (0.3 cm.), and it should extend beyond the borders of such areas. This then is covered with strips of the zinc acetate impregnated gauze, over which a pressure bandage is applied. Alternatively, the gel may be applied to the gauze, which is then placed over the injured area with the gel side in apposition to the wound. In first-degree burns or burns that exhibit only erythema, the dressing usually is removed the following day. In superficial second-degree burns, the dressing may be left intact until healing occurs. At that time the dressing will drop away from the wound readily. Earlier removal can be accomplished by soaking the dressing with warm isotonic sodium chloride solution. In deep second and third-degree burns, where grafting may be necessary, the surface frequently is ready for grafting within 9 to 12 days. In such cases it is advantageous to hasten removal of necrotic tissue by re-dressing once during this period. In severe burns, the

gel film separates readily after the dead skin becomes lysed. It is not necessary to use occlusive bandages on the hands, arms or face or in other areas where this is not feasible. Gauze is applied longitudinally to the extremities, rather than encircling the limb, to avoid abnormal constriction or pressure at vulnerable points. For small or facial burns, the gel and gauze may be applied as a patch without elastic bandage.

HYNSON, WESTCOTT & DUNNING, INC.

Zinax Burn Dressing: 22 18 cc. tubes of zincasate gel packaged with 10 gauze pads and 118.3 cc cans of zincasate gel packaged with 2 yards of gauze. The gauze is impregnated with approximately 30 per cent zinc acetate by weight.

U. S. patent 2,579,367.

DERMAL DRYING AGENTS

Sulfur ointments have long been used on the skin, especially in seborrheic dermatitis, where they produce drying and mild irritation. Selenium, which is just below sulfur in the periodic system, presumably acts similarly but apparently is more potent.

Selenium sulfide is insoluble in water and organic solvents. It is practically insoluble in water and organic solvents. Selenium sulfide reacts with aqua regia to give a clear solution.

have the formula Se_nS_m where n plus m equals 8

Physical Properties—Selenium sulfide is a dull reddish-orange to dull brown, amorphous powder. It is odorless, or has a slight sulfide odor, is tasteless and decomposes at about 100° . It is practically insoluble in water and organic solvents. Selenium sulfide reacts with aqua regia to give a clear solution.

Actions and Uses.—Selenium sulfide is employed only externally as a liquid suspension for application to the scalp in the treatment of seborrheic dermatitis and the control of seborrhea sicca (dandruff). It may be useful to a lesser extent in the management of psoriasiform seborrhea, seborrhea oleosa, acne vulgaris and juvenile acne.

degree. Experimental studies indicate that the amount absorbed, when applied as recommended below, is not much greater than the traces that may be present in the average diet. Selenium sulfide is highly toxic if taken orally and patients should be instructed to wash their hands and clean beneath the finger nails to remove all traces of the drug following each external application. The danger of accidental poisoning should be emphasized, and each patient should be warned to keep the drug out of the reach of children. Patients should be advised not to repeat applications unless directed by the physician. External use so far has not revealed any case of intoxication attributed to selenium sulfide. Sensitivity reactions which have been reported in some instances are believed caused by the detergent, alkyl aryl sodium sulfonate,

which is present in the commercially available suspension of the drug, although sensitivity to the drug itself rarely may be encountered

Dosage.—Selenium sulfide is applied externally as a suspension containing 2.5 per cent of the agent. For application to the scalp, the hair should be shampooed first with ordinary soap and rinsed. From 5 to 10 cc of the suspension then is applied by light massage with a small amount of warm water to make a lather. This is allowed to remain in contact with the scalp briefly, then rinsed and the application repeated. The agent should remain in contact with the scalp for a total of at least 5 minutes. The second application should be followed by three or four rinses to remove all traces of the agent. It is recommended usually that such applications be made twice weekly for 2 weeks and then once weekly or less often as indicated.

ABBOTT LABORATORIES

Suspension Salsun Sulfide: 118.3 cc bottles. A buffered, stabilized suspension containing a detergent and 25 mg. of selenium sulfide in each cubic centimeter.

U S patent 2,694,669 U S trademark 570,750

GOLD COMPOUNDS

The clinical use of gold salts in the treatment of arthritis has been in vogue since 1927, and has come to be recognized by many rheumatologists as having some value in selected and carefully supervised cases of progressive rheumatoid arthritis unrelieved by older and safer methods of treatment. Its therapeutic mechanism is not understood. According to one review on this subject (*Ann Int Med* 39 498 [Sept 1 1953]), corticotropin, cortisone and hydrocortisone have come into wide use in rheumatoid arthritis, and phenylbutazone has come into perhaps even wider use. These agents have replaced gold compounds to some extent, but gold is still considered a desirable adjunct or alternative by many physicians. Several gold preparations now available offer the advantage of lesser toxicity over the older gold sodium thiosulfate. According to the editorial review of Philip S. Hench (*Ann Int Med* 26 618 [April 1947]), with gold alone over half of the reported patients obtain symptomatic relief, complete in up to a sixth. Up to three-fourths of the improved cases relapse after a time, but may again improve under further treatment. The improvement usually does not begin until the gold injections have been continued for 1 to 3 months. This makes it difficult to assign a specific value to the gold treatment, especially as rheumatoid arthritis is potentially reversible without gold. Some skeptical observers consider the results about equal, with or without gold, but more conclude that gold plays a positive role, since the successes generally have been scored on patients in whom other measures have failed. The few control series, including a "blindfold" test, also note improvement rates five to ten times higher with gold than without. However, these chances of usually partial success must be weighed against

Physical Properties.—Aurothioglycanide is a grayish-yellow powder. It is insoluble in acids, bases, benzene, ether, chloroform and water.

Actions and Uses.—Aurothioglycanide, a water-insoluble gold compound, is used for the treatment of rheumatoid arthritis on the same basis and subject to the same precautions as water-soluble salts of gold (See the general statement on gold compounds.) Aurothioglycanide is absorbed more slowly from the

vision, repeated laboratory examinations which will reveal signs of gold intoxication and avoidance of exposure to sunlight, ultra-violet rays or x-rays are essential as with the use of other forms of chrysotherapy.

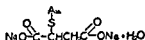
Dosage.—Aurothioglycanide is administered into the gluteal muscle by injection of a suspension in oil. The initial dose should not exceed 25 mg. This is increased gradually as tolerated by increments of not more than 25 mg administered at weekly intervals for 22 weeks. However, a maximum single dose of 150 mg. should not be exceeded. When untoward effects are observed, the schedule of weekly injections should be interrupted until such manifestations have disappeared.

ENDO PRODUCTS, INC.

Suspension Lauron in Oil: 5 and 10 cc vials. A suspension in sesame oil containing 50 and 150 mg of aurothioglycanide in each cubic centimeter.

U. S. patent 2,451,841. U. S. trademark 398,432.

GOLD SODIUM THIOMALATE-N.F.—Myochrysine (SHARP & DOHME)—Disodium aurothiomalate—"Gold Sodium Thiomalate yields not less than 93.3 per cent and not more than 101.5 per cent of $C_4H_3AuNa_2O_4S \cdot H_2O$ " N.F. The structural formula of gold sodium thiomalate may be represented as follows:



Physical Properties.—Gold sodium thiomalate is a fine, white to yellowish-white powder with a metallic taste. It is very soluble in water and practically insoluble in alcohol and in ether. Aqueous solutions of gold sodium thiomalate are colorless to pale yellow. The pH of a 5 per cent solution is between 5.8 and 6.8.

Actions and Uses.—Gold sodium thiomalate, like other gold salts, is indicated for the treatment of established cases of active rheu-

of other arthritides. See also the statement on gold compounds.

Dosage.—For active rheumatoid arthritis, an initial intramuscular dose of 10 to 15 mg. is suggested in all patients to test tolerance to the drug. Subsequent doses of 15 to 50 mg. at weekly intervals.

For chronic arthritis, 2,000 mg. as a single dose, or 1,000 mg. is considered given, with an in-

creased dose of 5 mg., in a maximum of 50 mg. for men, usually is recommended.

Toxic reactions generally are minimized by the use of weekly doses not to exceed 25 mg. Transient flushing of the face with giddiness and vertigo may be observed following administration.

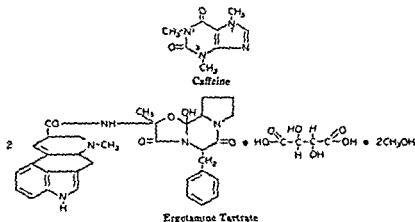
SHARP & DOHME, DIVISION OF MEXEL & Co, Inc

Solution Myochrysin. 1 cc ampuls. A solution containing 10, 25, 50 or 100 mg of gold sodium thiomalate, equivalent to 5, 12.5, 25 and 50 mg of gold, respectively. Preserved with 0.5 per cent benzyl alcohol.

U. S. trademark 318,890 assigned to Societe des Usines Chimiques Rhone-Poulenc, Paris, France.

AGENTS FOR RELIEF OF MIGRAINE

ERGOTAMINE WITH CAFFEINE—Cafergot (SANDOZ).—A mixture containing about 1 part of Ergotamine Tartrate-U.S.P. and 100 parts of anhydrous Caffeine-U.S.P. The structural formulas of ergotamine tartrate and caffeine may be represented as follows:



Actions and Uses.—Certain investigators have reported that caffeine acts synergistically with ergotamine tartrate and, thus, lowers the dosage of ergotamine tartrate required for the relief of migraine. Experimental evidence indicates that the addition of

caffeine also reduces the toxicity of orally administered ergotamine tartrate.

The effect of the combination probably is brought about by constriction of the cerebral arteries during the vasodilatation phase of the migraine syndrome.

The use of ergotamine tartrate and caffeine is contraindicated in the presence of
or liver disease
be used prophylactically for
attacks.

Dosage—The smallest effective dose of the combination should be determined for each patient. The usual initial dose is 2 mg. of ergotamine tartrate and 200 mg. of caffeine. Subsequent doses of 1 mg. of ergotamine tartrate and 100 mg. of caffeine may be administered at ½-hour intervals if the migraine is not relieved. The total dose should not exceed 6 mg. of ergotamine tartrate and 600 mg. of caffeine.

SANDOZ CHEMICAL WORKS, INC.

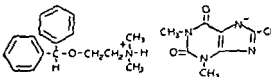
Tablets Cafergot: Each tablet contains 0.1 Gm. of caffeine and 1 mg. of ergotamine tartrate

U. S. trademark 528,520

MOTION SICKNESS REMEDIES

Through the years many preparations have been used for motion sickness. Until recently the most popular were barbiturates, chlorobutanol and various autonomic drugs, especially scopolamine. From extensive trials during World War II and the years following, it has been demonstrated rather clearly that scopolamine and certain of the antihistamines possess greater potency than the other drugs. Therefore, they now have replaced most of the older preparations in the treatment of motion sickness. Scopolamine and a number of the antihistamines, for instance dimenhydrinate, diphenhydramine and prophenpyridamine, all show about the same degree of action. At times the more diverse side effects of scopolamine make it less satisfactory than the antihistamines, but it is still a substantial alternative or adjuvant.

DIMENHYDRINATE-U.S.P.—*Dramamine* (SEARLE)—2-(Benzohydroxy)-N,N-dimethylethylamine 8-chlorotheophyllinate—"Dimenhydrinate contains not less than 53 per cent and not more than 55.5 per cent of diphenhydramine ($C_{17}H_{21}NO$), and not less than 44 per cent and not more than 47 per cent of 8-chlorotheophylline ($C_7H_7ClN_4O_2$)."
U.S.P. The structural formula of dimenhydrinate may be represented as follows:



Physical Properties.—Dimenhydrinate is a crystalline, white, odorless powder. It is freely soluble in alcohol and chloroform, soluble in benzene, sparingly soluble in ether and slightly soluble in water. It melts between 102° and 107°. The pH of a saturated solution is between 6.8 and 7.3.

Actions and Uses.—Dimenhydrinate is a chlorotheophylline salt of the histamine antagonist, diphenhydramine. Its actions are similar to the antihistamine compounds and it shares with them the ability to produce mild sedation of central nervous system origin. Experimentally, the antihistaminic potency of dimenhydrinate is approximately one and one-half times as effective as diphenhydramine. The spasmolytic action of dimenhydrinate is comparatively low and is attributed to its relative insolubility in water. Intravenous injection of the drug in experimental animals produces transient lowering of blood pressure and brief stimulation of respiration. Acute toxicity studies in rats indicate that the LD₅₀ dose is about 150 mg per kilogram of body weight, depending on the route of administration. Subacute and chronic toxicity studies in experimental animals have not revealed microscopic evidence of pathologic changes in the heart, liver, kidney or brain. Because of the antihistamine component the danger of prolonged administration should be kept in mind, particularly with respect to possible toxic effects on the hemopoietic system.

Dimenhydrinate is useful in the prevention or treatment of motion sickness. The mechanism of its action in this condition has not been explained completely but apparently is attributable to the diphenhydramine portion of the molecule. It is effective in a high percentage of cases of seasickness, car and train sickness and, to a lesser extent, in airsickness, in which the drug is still a valuable remedy.

The use of dimenhydrinate for the control of nausea and vomiting in motion sickness has led to its use to control these symptoms and that of vertigo in other conditions. Thus, it has been found useful for the management of vertigo in Meniere's syndrome, radiation sickness, hypertension, fenestration procedures, labyrinthitis and vestibular dysfunction associated with streptomycin therapy. It also is useful in the symptomatic control of nausea and vomiting associated with narcotization, electroshock therapy and incidental to therapy with certain other drugs such as chlortetracycline. Premedication may be useful as a preventive in electroshock therapy.

Dosage.—Dimenhydrinate is administered orally or rectally. The usual oral dose for adults is 50 mg, taken ½ hour before departure, for the prevention of motion sickness. This dose may be repeated before meals and on retiring for the duration of the journey. Doses up to 100 mg may be taken every 4 hours for motion sickness or to control nausea and vomiting in other conditions, but larger doses are more prone to produce drowsiness. For oral administration to children, two or three times daily: 5 to 8 years of age, 12.5 to 25 mg; 8 to 12 years of age, 25 to 50 mg; over 12 years, 50 to 100 mg. The same doses may be administered rectally by insertion of the tablet or other suitable form for the

treatment of motion sickness or the control of nausea and vomiting in other conditions.

G. D. SEARLE & Co.

Liquid Dramamine: 473 cc. bottles. A solution containing 3.1 mg. of dimenhydrinate in each cubic centimeter.

Tablets Dramamine: 50 mg.

U. S. patent 2,499,058 U. S. trademark \$27,862.

WOUND PROTECTIVES

Drugs with a stimulating action on wound healing have long been desired, and many preparations, such as scarlet red ointment, have been reputed to possess such power. It is probably safe to assume, however, that no substances presently available can promote growth at a more rapid rate than that of normal, optimal healing. Nevertheless, preparations that act as bland protectives may be conducive to wound healing through prevention of crusting and trauma and may reduce offensive odors in some instances.

WATER-SOLUBLE CHLOROPHYLL DERIVATIVES.—*Chloresium* (RYSTAN).—Water-soluble derivatives of chlorophyll consist chiefly of the copper complex of the sodium and/or potassium salts of saponified chlorophyll

Physical Properties.—Water-soluble chlorophyll derivatives present as pasty solids and/or sodium salts occur as a blue-black glisten-

They are freely soluble in chloroform and very slightly soluble in ether. A 1 per cent solution is dark green and has a pH between 9.5 and 10.7

Actions and Uses.—A mixture of the water-soluble derivatives of chlorophyll is employed as a bland, soothing, nonirritating preparation for topical application. A solution or ointment is used for deodorization, normal tissue repair and relief of itching in wounds, ulcers, burns and dermatoses. It does not exert a significant disinfectant action and the mechanism of its deodorant effect on foul-smelling chronic lesions is not clear. Such lesions, which are due primarily to chronic infection, may require surgical interven-

Water-soluble chlorophyll in granulating wound base al repair of tissues. Conclusive evidence is lacking that chlorophyll derivatives stimulate granulation or epithelization beyond the normal rate of healing, but they may overcome retarding factors so as to bring the healing rate up to or toward the normal rate

Dosage.—A solution containing 0.2 per cent water-soluble chlorophyll derivatives is applied topically to the affected areas once, or several times daily, as desired

An ointment containing 0.5 per cent may be spread over affected areas and covered with fine-mesh gauze or other dressing. Applications are repeated at each change of dressing.

RYSTAN COMPANY, INC.

Ointment Chloresium 0.5%: 28.35 and 113.4 Gm tubes; 454 Gm jars. An ointment containing 5 mg of water-soluble chlorophyll derivatives in each gram of water-miscible base.

Solution Chloresium 0.2%: 59.14, 236.5 and 946.3 cc. bottles. A solution containing 2 mg of water-soluble chlorophyll derivatives in each cubic centimeter.

U. S. patents 2,120,667 and 2,434,649 U. S. trademark 408,787.

530; Dimothyn, 407; Mercurphylline (Sodium), 384; Nicotinamide, 584; Thiamine Hydrochloride, 593; Trionamide, 129.

GANE'S CHEMICAL WORKS, INC., 611-641 Broad St., Carlstadt, N. J.—
Phenindione, 295, Secobarbital, 335, Secobarbital Sodium, 336

GRIGY PHARMACEUTICALS, DIVISION OF GRIGY CHEMICAL CORPORATION,
220 Church St., New York 13, N. Y.—Butarolodin, 21; Tromexan
Ethyl Acetate, 291.

GILBERT, ALLEN & COMPANY, 2380 Palm Ave., Hialeah, Fla.—Testosterone
Propionate. 483.

GOLD LEAF PHARMACEUTICAL COMPANY, INC., 36 Lawton St., New Rochelle, N. Y.—Amphetamine Sulfate, 220; Corlutone, 455; Diethylstilbestrol, 448; Menadione, 604; Mephesisin, 556; Para-Pas, 96; Para-Pas Sodium, 98; Sodium Ascorbate, 597; Testosterone Propionate, 483; Thiamine Hydrochloride, 593.

HAMILTON LABORATORIES, INC., THE, 420 Lexington Ave., New York 17,
N. Y.—Merobenzyl Nitrate. 64

HARROWER LABORATORY, INC., THE, 930 Newark Ave., Jersey City, N. J.—
Mucotin. 407

HARY DRUG CORPORATION, 25 N E. 25th St., Miami 30, Fla.—Ribo-

HYNSON, WESTCOTT & DUNNING, INC., Baltimore 1, Md.—Aluminum
Penicillin, 164, BAL, 614, Lutrexin, 453, Zinax Burn Dressing, 618

INTERMEDICO CORPORATION, 118 Cherry Lane, Floral Park, Long Island,
N. Y.—Pasmed Sodium, 98

IVES-CAMERON COMPANY, DIVISION OF AMERICAN HOME PRODUCTS CORP.,
1401 Walnut St., Philadelphia 2, Pa.—Meonine, 517; Nicotinic Acid,
585, Nicotinic Acid Amide, 584, Oleo Vitamin A, 574; Pyridoxine
Hydrochloride, 588, Riboflavin, 590, Thiamine Hydrochloride, 594.

JACKSON-MITCHELL PHARMACEUTICALS, INC., 10401 W. Jefferson Blvd,
Culver City, Calif—Thylose Sodium, 414

KEITH-VICTOR PHARMACAL COMPANY, 1825 Chouteau Ave., St. Louis 3, Mo.—Amphetamine Phosphate, 218, Amphetamine Sulfate, 220, Diethylstilbestrol, 448, Folic Acid, 582, Mannitol Hexanitrate, 320, Niacin, 585; Niacinamide, 584; Pyrilamine Maleate, 15, Riboflavin, 591, Secobarbital Sodium, 336, Sulfadiazine, 110, Thiamine Hydrochloride, 594, Zinadon, 101

KENDALL, C. B., COMPANY, 2039 Madison Ave., Indianapolis 6, Ind.—
Mephengsin, 556

Kirk, C. F., COMPANY, 521-523 W. 23rd St., New York 11, N. Y.—
Mephensesin, 536
Hemomin, 578, Mersalyn, J87, Testosterone Propionate, 483

- Merdiazine, 130; Orestralyne, 442; Sulfadiazine, 111; Syndrox Hydrochloride, 232.
- MEAD JOHNSON & COMPANY, Evansville 21, Ind.—Amigen, 515; Levugen, 527; *Oleum Percomorphum with Other Fish Liver Oils and Viosterol*, 609.
- MEDICAL CHEMICALS, INC., 406 E. Water St., Baltimore 2, Md.—Iso-Par, 82.
- MERCK & Co, INC., Rahway, N. J.—Mandelic Acid, 102; Niacin, 586; Niacin chloride
- MERRELL,
—Ceeg
Sulfat
Bisulf
Ascorb
187, 5
Tyvid,
- METROPOLITAN
Testos
- MEYER C.
Estron
Sodium
- MICHAEL F.
S. Eli
Humar
Immune Serum, 492
- MILLER, E. S., LABORATORIES, INC., P. O. Box 2302, Terminal Annex, Los Angeles 54, Calif.—Diethylstilbestrol, 449; Estrone, 437; Menadione, 605; Neostigmine Methylsulfate, 261; Nikethamide, 347; Pyridoxine Hydrochloride, 588; Sul-Di-Mill, 127; Sulfadiazine, 111; Testrone, 479; Thiamine Hydrochloride, 594; Tolulox, 556.
- MILWAUKEE BLOOD CENTER, INC., 763 N. 18th St., Milwaukee 3, Wis.—Measles Immune Serum, 491; Normal Human Plasma, 281; Pertussis Immune Serum, 492; Scarlet Fever Immune Serum, 492
- NATIONAL DRUG COMPANY, Haines and McCallum Sts., Philadelphia 44, Pa.—Aminonate, 516; Combined Diphtheria and Tetanus Toxoids (Alum Precipitated), 499; Diphtheria and Tetanus Toxoids, Alum Precipitated, and Pertussis Vaccine Combined, 507; Diphtheria Toxoid, Alum Precipitated, and Pertussis Vaccine Combined, 505; Influenza Virus Vaccine, Polyvalent, 501; Mannitol Hexanitrate, 320; Nicotinic Acid, 586; Pertussis Vaccine, 502; Pertussis Vaccine (Alum Precipitated), 503; Tetanus Toxoid (Alum Precipitated), 504
- NEP
vera Park, Yonkers 2, N. Y.—
hydrochloride, 16; Pyridine, 101.
Pl., Los Angeles 38, Calif—
- NOV
1-23 Atlantic Ave., Brooklyn 7,
N. Y.—Amylase Hydrochloride, 51, Monocaine Formate, 43, Monocaine Hydrochloride, 44.
- OHIO CHEMICAL & SURGICAL EQUIPMENT COMPANY, 1400 E. Washington Ave., Madison 10, Wis.—Cyclopropane, 36
- ORGANON, INC., Orange, N. J.—Bifactorin, 580; Dimenformon Benzoate, 439; Doca Acetate, 419; Liqueamin Sodium, 293; Lynoral, 442; Muralin, 520; Oranixon, 356
- ORTHO PHARMACEUTICAL CORPORATION, Raritan, N. J.—Ortho-Creme Vaginal Cream, 353; Ortho-Gynol Vaginal Jelly, 354.
- PARSONS
New York 13, N. Y.—Isoniazid,
at the River, Detroit 32,
in Hydrochloride, 197,
Combined Diphtheria-
(Aluminum Phosphate
pharsen, 211; Metapom
xycel, 298; Pertussis

PASADENA RESEARCH LABORATORIES, INC., 2107 E. Villa, Pasadena 8, Calif.—Thiamine Hydrochloride, 594

PATCH, E. L. COMPANY, THE, Stoneham 80, Mass.—Alunox, 407, Glythionate, 393

PENICK, S. B. & COMPANY, 50 Church St., New York, N. Y.—Tyrothricin, 56

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC., 630 Flushing Ave., Brooklyn 6, N. Y.—Bacitracin, 138, Combistrep, 196; Cortril, 427, Cortril Acetate, 429, Cotinazin, 101, Dihydrostreptomycin Sulfate, 183, Estrone, 437, Magnamycin, 140, Neodrol, 478, Permapen, 166, Polymyxin B Sulfate, 180, Potassium Penicillin G, 171; Procaine Penicillin G, 173, Streptomycin Sulfate, 187, Terramycin Hydrochloride, 18, Tetracycline Hydrochloride, 18

PHILADELPHIA HOSPITAL OF PHILADELPHIA, 17, N. Y.—

PHILADELPHIA HOSPITAL OF PHILADELPHIA, 17, N. Y.—Pertussis Immune

PHYSICIANS' DRUG & SUPPLY COMPANY, Third & Callowhill Sts., Phila-

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PHYSICIANS' DRUG & SUPPLY COMPANY, Third & Callowhill Sts., Phila-

- RIKER LABORATORIES, INC., P. O. Box 3157, Terminal Annex, Los Angeles 54, Calif.—Veriloid, 311.
- ROBINS, A. H., COMPANY, INC., 1407 Cummings Drive, Richmond 20, Va.—Robalate, 407.
- ROERIC, J. B., & COMPANY, DIVISION OF CHAS. PFIZER & COMPANY, INC., 536 Lake Shore Drive, Chicago 11, Ill.—Thiamine Hydrochloride, 594; Vibalt, 579.
- ROER, WILLIAM H., INC., 214 S. Fifth St., Philadelphia 6, Pa.—Aluminum Hydroxide, 402, Carfusin, 81; Diethylstilbestrol, 449; Disulfyn, 127, Mannitol Hexanitrate, 321; Sodium Ascorbate, 598, Sulfadiazine, 111, Thiamine Hydrochloride, 594, Thylogen Maleate, 15; Vitamin B₁₂, 579.
- ROWELL LABORATORIES, INC., Baudette, Minn.—Burbot Liver Oil, 607.
- RYSTAN COMPANY, 7 N MacQuesten Pkwy., Mount Vernon, N. Y.—Chloresium, 627.
- SANDOZ PHARMACEUTICALS, DIVISION OF SANDOZ CHEMICAL WORKS, INC., Route 10, Hanover, N. J.—Cafergot, 624; Digilanid, 304; Methergine Tartrate, 537.
- SCHENLEY LABORATORIES, INC., 350 Fifth Ave., New York 1, N. Y.—Potassium Penicillin G, 171, Sodium Ascorbate, 598; Titalac, 404.
- SCHERING CORPORATION, 2 Broad St., Bloomfield, N. J.—Chlor-Trimeton Maleate, 10, Cortogen Acetate, 424, Estinyl, 442, Prantal Methylsulfate, 267, Priodax, 368, Sodium Sulamyd, 117; Solganal, 621; Sulamyd, 116; Tricombisul, 125, Trimeton Maleate, 14.
- SCHIEFFELIN & COMPANY, 16-30 Cooper Square, New York 3, N. Y.—Benzestrol, 452, Cyclogyl Hydrochloride, 264, Damlone, 295; Merbak, 62.
- SCHMID, JULIUS, INC., 423 W 55th St., New York 19, N. Y.—Ramses Vaginal Jelly, 354.
- SCHWARZ LABORATORIES, INC., 230 Washington St., Mount Vernon, N. Y.—Methiacil, 520.
- SEARLE, G. D. & Co., P. O. Box 5110, Chicago 80, Ill.—Aldase, 395; Bactocin, 370, Dactin, 314, Deminon, 426; Hydrochlorol, 11.
- SHA—
 broad St.
 Benemid,
 substances
 oxide, 48;
 Hydro-
 Globulin,
 concentrated
 Mecholyl
 33; Myo-
 chrysine, 623, Nalime, 34, Neo-Valelgan, 10, Protamine Human
 sodium Peni-
 streptomycin
 Ifamerazine,
 xoid (Alum
 Urecholine

 15, Mich—

 ick, N. J.—
 onorn Sul-
 idit, 447
- SMITH-DORSEY, DIVISION OF THE WANDER COMPANY, Lincoln, Neb.—Doraxamin, 407, Dors Dorsulfas, 125, Pasar, 483.
- SMITH, KLINE & FRENCH, Philadelphia 1, Pa.—Benzed Sulfate, 222, Paredrin-ride, 47.
- SMITH, UPSEDER, COMPANY, 529 S Seventh St., Minneapolis, Minn.—Pyrethrum, 93.
- SQUIRE, E. R., & SONS, DIVISION OF OLIN MATHIESON CHEMICAL CORPORATION, 745 Fifth Ave., New York 22, N. Y.—Amnestrogen, 443;

STOP =

STRA - ■ ■ ■

Succ =

Seite 1

Hydrochloride. 595

356
TABLAX COMPANY, 32 Union Square, New York, N. Y.—Marvosan Creme,

TABLET ROCK LABORATORIES, Greenville, S C—Choline Chloride, 529.
Methionine, 517

TESTAGAR & COMPANY, INC., 1354 W. Lafayette, Detroit 26, Mich—
Heparin Sodium, 293, Sodium Ascorbate, 598, Testosterone Pro-
mone, 483

THOMPSON, MARVIN R., Inc., 67 Greenwich Ave., Stamford, Conn.—
Sulfadiazine, 111. Sulfatriazine, 130. Vitamin B Complex, 576

T

ULMER PHARMACEUTICAL COMPANY, 1400 Harmon Place, Minneapolis 3, Minn ---
Mephensolin. 557

Uyehon COMPANY, INC., Kalamazoo 99, Mich.—Adrenal Cortex Extract,
417, Aluminum Hydroxide, 176, procaine, 176, Cer O Collin
475, Cortef, 427, Cortef A

thionamide, 344. Tyrosine chloride, 241. Riboflavin, 591. 112. Sulfamerazine, 114. Testosterone Propionate, 484. 268.

U. S. STANDARD PRODUCTS COMPANY, Woodworth Wis.—Diphtheria and Tetanus Toxoids with Pertussis Vaccine, Combined, 507, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Combined Alum Precipitated, 508, Pertussis Vaccine 503, Tetanus Toxoid, 497, Tetanus Toxoid (Alum Precipitated), 498.

U. S. VITAMIN CORPORATION, 250 E. 43rd St., New York 17 N. Y.—
Choline Dihydrogen Citrate, 530. Menadione, 605. Methionine, 517.
Niacin, 586. Niacinamide, 584. Pyridoxine Hydrochloride, 588. Ribo-
flavin, 591. Thiamine Hydrochloride, 595. Vitamin A Drops, 575.

VALE CHEMICAL COMPANY, INC., THE, 814-816 Gordon St., Allentown, Pa.—Aluminum Hydroxide, 402; Dexoval Hydrochloride, 232; Diazepam, 19; Niacin, 586; Nicotinamide, 584; Riboflavin, 591; Sulfadiazine, 112;

ain St., Richmond 4, Va.—Oradiol, Hydrochloride, 595; Trifonamide,

Aluminum Hydroxide, 402; Benzylol Fuchsin Paint, 81; Undesol, 87. 41 Union Square, New York 3,

ichester Ave., St. Louis 10, Mo.—

st St., Chicago 10, Ill.—Vitamin B

11th Ave., New York 36, N. Y.—parin Sodium, 294; Neostigmine icillin G, 174; Progesterone, 455, Ascorbate, 598; Testosterone Pro-

WALKER LABORATORIES, INC., Bradford Rd., Mount Vernon, N. Y.—Bacimycin, 193, Choline Dihydrogen Citrate, 530, Folic Acid, 582, Hedulin, 295, Heparin Sodium, 294, Hexavitamin, 609; Methionine, 517, Nicotinamide, 584, Nicotinic Acid, 586; Concentrated Oleo Vitamin A and D, 608, Riboflavin, 591; Thiamine Hydrochloride, 595. WALLACE & TIERNAN INC., 25 Main St., Belleville 9, N. J.—Azochloramid, 58; Salundek (New), 86, Sodium Sotradecol, 551, Undecylenic Acid, 85; Zincundecate, 87

WAMPOLE, HENRY K., & COMPANY, INC., 440 Fairmount Ave., Philadelphia 23, Pa.—Sulfatryl, 131

WARNER CHILCOTT LABORATORIES, DIVISION OF WARNER-HUDNUT, INC., 113 W. 18th St., New York 11, N. Y.—Cellothyl, 412; Diatrine am Chloride, 315; Peri-

259.
Goodale St., Columbus ne Hydrochloride, 232,

ienestrol, 446; Gitaligin, 574, Testosterone Pro-

WHITTAKER LABORATORIES, INC., 898 Washington St., Peekskill, N. Y.—Cooper Creme, 355

WHITTIER LABORATORIES, 919 N. Michigan Ave., Chicago 11, Ill.—Chlorothen Citrate, 10

WILSON LABORATORIES, THE, 4221 S. Western Ave., Stock Yards Station, Chicago 9, Ill.—Corticotropin, 471, Gastric Mucin, 409; Purified Corticotropin-Gel, 472

WINTHROP-STEARN, INC., 1450 Broadway, New York 18, N. Y.—Adanon Hydrochloride, 29, Aralen Phosphate, 199; Atabrine Hydrochloride, 201, Avertin, 38, Creamalin, 402, Demerol Hydrochloride, 27; Diethylstilbestrol, 449; Diodrast Compound, 373; Diodrast Concentrated, 375, Drisdol, 601; Evipal Sodium, 330; Euadin, 206, Isuprel Hydrochloride, 227, Levophed Bitartrate, 230; Mebaral, 332, Milibis, 208, Parenamine, 515; pHisoHex, 71, Pontocaine Hydrochloride, 53, Potassium Penicillin G, 172; Salyrgan (Sodium) Theophylline, 387; Sulfadiazine, 112, Telepaque, 369, Thiamine Hydrochloride, 595; Zephiran Chloride, 75.

WYETH LABORATORIES, INC., 1401 Walnut St., Philadelphia 2, Pa.—Amphojel, 403, Basaljel, 406, Bicillin, 166; Bornate, 89; Conestron, 443, Combined Diphtheria-Tetanus Toxoid (Alum Precipitated), 499, Pertussis Vaccine, 503, Phosphaljel, 403; Picragol, 65; Plavolex, 283, Propionate-Caprylates Compound, 83; Propion Gel, 84; Tetanus Toxoid (Alum Precipitated), 498, Thiomersin Sodium, 381, Wydase, 396.

General Index

(The brand and generic names of exempt and re accepted drugs are listed in the General Index with a reference to the last edition of *New and Non-official Remedies* in which actions, uses and dosage appeared)

- Absorbable Cotton or Gauze, 296
 Dusting Powder, 539
 Gelatin Film, 540
 Sponge, 295
 Absorbent Ointment Base, 543
 Acceptance, Rules Governing, xvii
 Acetarsone-N.F. (see N.N.R. 1950)
 Acet-Dia-Mer-Sulfonamides (see Sulfacetamide, Sulfadiazine, and Sulfamerazine)
 Acetomerocetol, 61
 Acetpyrogall (see N.N.R. 1951)
 Acetyl Sulfisoxazole, 121
 Achromycin Hydrochloride, 190
 Acton Vitamin A, 574
 Acriflavine-N.F. (see N.N.R. 1952)
 Hydrochloride (see N.N.R. 1950)
 ACTH Injection, 469
 Acthar, 471
 Adanon Hydrochloride, 29
 Adding Analgesics, Nonopiate, 24
 Adrenal Cortex, 415
 Extracts, 417
 Injection, 417
 Cortical Extracts, 415
 Steroids, 416
 Adrenalin (see N.N.R. 1949)
 Adrenals, 415
 Adrenergic Blocking (Sympatholytic) Agents, 243
 (Sympathomimetic) Agents, 216
 Adrenocorticotrophin Injection, 469
 Aeroplast, 542
 Aerosporin Sulfate, 180
 Albumin, Normal Human Serum, 278
 Alcoholism, Agents for Treatment of, 610
 Aldarsone, 208
 Alglyn, 406
 Alidase, 395
 Alkagel, 401
 Alkavervir, 308
 Allergenic extracts, in allergy, 4
 Preparations (see N.N.R. 1950)
 Allergy, agents used in, 1
 Allylisopropylbarbituric Acid, 327
 Allylisopropylmalonylurea, 327
 N-Allylnormorphine Hydrochloride, 33
 Almagucin, 407
 Alphaprodine Hydrochloride, 24
 Al U-Creme, 401
 Aludrine Hydrochloride, 226
 Aluminum Carbonate, Basic, 404
 Glycinate, Basic, 406
 Aluminum Carbonate—(Continued)
 Hydroxide Preparations, 400
 Penicillin, 164
 Phosphate Preparations, 403
 Alurate, 328
 Alzinox, Magma, 407
 Amethocaine Hydrochloride, 52
 Amigen, 515
 Amino Acid and Protein Hydrolyzate Preparations, 511
 Acids, Individual, 516
 Aminoacetic Acid and Calcium Carbonate, 404
 Aminonol, 516
 Aminophylline-U.S.P. (see N.N.R. 1954)
 Aminopyrine N.F. (see N.N.R. 1949)
 Aminosalcylate Calcium, 97
 Sodium, 97
 Aminosalicic Acid, 95
 Derivatives, 95
 Aminosol, 514
 Amnestrogen, 443
 Amobarbital U.S.P. (see N.N.R. 1950)
 Sodium-U.S.P. (see N.N.R. 1950)
 Amodiaquin Hydrochloride, 196
 Amphetroxyn Hydrochloride, 231
 Amphetamine Phosphate, 217
 Sulfate, 218
 Dextro, 221
 Amphojel, 403
 Amylsine Hydrochloride, 51
 Amytal (see N.N.R. 1950)
 Sodium (see N.N.R. 1950)
 Anacidity, Agents Used for Determination of Gastric, 359
 Anaesthesia (see N.N.R. 1949)
 Analgesics, 19
 Anayodin (see N.N.R. 1950)
 Androlin, 479
 Anectine Chloride, 539
 Anesthesia (see N.N.R. 1949)
 Anesthetics, 35
 General, 35
 Local, 39
 Aneurine Hydrochloride, 591
 Anionic Agents, 72
 Antabuse, 612
 Antacids, 400
 Antagonists of Curariform Drugs, 567
 Antazoline Hydrochloride, 6
 Phosphate, 7

- Antepar Citrate, 94
 Anterior Lobe, 467
 Anthracene Derivatives, 612
 Anthralin, 612
 Antibacterial Agents, 54, 95
 Antibiotic Mixtures, 192
 Antibiotics, 54, 132
 Anticoagulants, 287
 Antifungal Agents, 79
 Antihemophilic Plasma (Human), 279
 Anti-Hemophilus Influenzae Type B Serum (Rabbit), 489
 Antihistamine drugs, dermatologic preparations of, xxxix
 Anti-infectives, evaluation of, xxxi
 Local, 54
 Systemic, 93
 Antimalarial Agents, 196
 Antimony Compounds, 203
 Antipedicular Agents, 87
 Antiprotosoan Agents, 201
 Antiscabious Agents, 90
 Antistine Hydrochloride, 7
 Phosphate, 8
 Antithyroid Drugs, 517
 Antivenin (Latrosectus Mactans), 490
 Apresoline Hydrochloride, 246
 Aprobarbital, 327
 Sodium, 328
 Aralen Phosphate, 199
 Argyn (see N.N.R. 1949)
 Aristol (see N.N.R. 1949)
 Arsenic Compounds, 206
 Pentavalent, 206
 Trivalent, 208
 Arsthol, 209
 Artane Hydrochloride, 271
 Ascorbic Acid-U.S.P. (see N.N.R. 1954)
 Injection, 596
 Aspogen, 406
 Atabrine Hydrochloride, 201
 Aureomycin, 142
 Calcium, 143
 Hydrochloride, 146
 Aurothioglucose, 621
 Aurothioglucanide, 621
 Autonomic Drugs, 215
 Avertin, 38
 Azochloramid, 38
 Azulfidine, 121

 Bacimycin, 193
 Bacitracin, 135
 -Neomycin, 192
 BAL, 614
 Balarsen, 210
 Banthine Bromide, 270
 Barbitol-N.F. (see N.N.R. 1949)
 Sodium-N.F. (see N.N.R. 1949)
 Barbituric Acid Derivatives, 323
 Barium Sulfate-U.S.P. (see N.N.R. 1949)
 Basaljel, 406
 Bases, Ointment, 542
 Basic Aluminum Carbonate, 404
 Glycinate, 406
 Beadox Hydrochloride, 588
 Benadryl Hydrochloride, 11
 Benemid, 617
 Benodaine Hydrochloride, 364
 Benoxinate Hydrochloride, 42
 Benzilate, 92
 Benzalkonium Chloride, 74
 Benzathine Penicillin G, 164
 Benzazoline Hydrochloride, 250
 Benzedrex, 240
 Benzedrine Sulfate, 221
 Benzene Hexachloride, Gamma, 90
 Benzestrol, 452
 Benzethonium Chloride, 75
 Benzpyriminium Bromide, 258
 Benzyl Alcohol-N.F. (see N.N.R. 1950)
 Benzoate, 91
 -*Chlorophenothane-Ethyl*
 Aminobenzoate, 87
 Penicillin Potassium, 168
 Sodium, 174
 Beta estradiol Benzoate, 438
 Bethanechol Chloride, 253
 Bevidox, 578
 Bicillin, 166
 Bifactor, 580
 Bilein (see N.N.R. 1949)
 Bio-Sorb, 540
 Bishydroxycoumarin, 287
 Bismuth Compounds, 211
 -*Glycolylarsanilate*, 207
 Magma-N.F. (see N.N.R. 1949)
 Potassium Tartrate-N.F. (see N.N.R. 1952)
 Sodium Tartrate (see N.N.R. 1952)
 Thioglycollate (see N.N.R. 1952)
 Triglycollamate, 212
 Bistrimate, 213
 Bistrium Bromide, 313
 Chloride, 315
 Bi-Sulfazine, 127
 Bisulfon, 127
 Bivalent Gas Gangrene Antitoxin-N.F. (see N.N.R. 1952)
 Blocking Agents at the Renal Tubules, 614
 Blood Derivatives, 278
 and Plasma Substitutes, 274
 Formation and Coagulation, Agents Affecting, 286
 Grouping, Agents for, 284
 Volume, Agents Used for Determination of, 357
 Blutene Chloride, 300
 Bornate, 89
 Brewer's Yeast (see N.N.R. 1952)
 Bromisovalum-N.F. (see N.N.R. 1951)
 Bromsulphalein Sodium (see N.N.R. 1952)
 Bromural (see N.N.R. 1951)
 Bronchodilators, in allergy, 2

- Buffonamide, 125
 Bulk Drugs, xviii
 Burbot Liver Oil, 607
 Burn Dressings, 617
 Bursoline, 60
 Butabarbital Sodium, 328
 Butacaine Sulfate N F (see N N R 1950)
 Butamben Picrate (see N N R 1951)
 Butazolidin, 21
 Butesin (see N N R 1950)
 Picrate (see N N R 1951)
 Butethal-N F (see N N R 1951)
 Butethamine Formate, 43
 Hydrochloride, 43
 Butisol Sodium, 329
 Butyl Aminobenzoate N F (see N N R 1950)
 Butyn Sulfate (see N N R 1950)
 Cafergot, 624
 Caffeine, 623
 Ergotamine with, 623
 Calciferol, 399
 Calcium Aminoacrylate, 97
 Carbonate and Aminoacetic Acid, 404
 Compounds, 522
 Gluconate U S P (see N N R 1947)
 Iodobehenate N F (see N N R 1949)
 Levulinate, 522
 Para Aminoacrylate, 97
 Phosphate, Tribasic-N F (see N N R 1947)
 Propionate, 82, 83
 Salicylate, Theobromine-N F (see N N R 1948)
 Caminoids 516
 Camouquin Hydrochloride 197
 Caprylate Propionate Mixtures, 82
 Caprylic Acid, 82
 Compound 80
 Cathacrylamine Resins 321
 Cathacrylic Resin, Quinine 359
 Carbamylmethyleholine Chloride, 254
 Carbarone U S P (see N N R 1954)
 Carbinoxamine Maleate, 8
 Carbohydrates 526
 Carbol Fuchsin Paint, 81
 Carbomycin 119
 Carbon Dioxide U S P (see N N R 1947)
 Carbo-Resin, 526
 Carbowax 400, 543
 1000, 543
 1500, 544
 1540, 544
 4000, 544
 Carboxymethylcellulose Sodium, 414
 Cardiovascular Agents, 301
 Carfium 81
 Carotene (see N N R 1954)
 Castellani's Paint, 81
 Cathartics and Laxatives, 409
 Cationic Agents, 72
 Cebione (see N N R, 1954)
 Ceepryn Chloride, 77
 Celliothyl, 412
 Cellulase, Oxidized, 296
 Cellulose Acid, 296
 Central Nervous System Depres-
 sants, 323
 Stimulants, 345
 Cer-O Cillin Chloroprocaine, 176
 Potassium, 177
 Cetazine, 125
 Cetyl Pyridinium Chloride, 76
 Ceveex (see N N R 1954)
 Chinofoan-U S P (see N N R 1950)
 Chloramine-T-N F (see N N R, 1949)
 Chloramphenicol, 140, 141
 Chlorazene (see N N R 1949)
 Chlorcyclizine Hydrochloride, 9
 Chloretum, 627
 Chloretone (see N N R, 1950)
 Chlorine Derivatives 36
 Chloriodized Oil, 367
 Chlormerodrin, 379
 Chloroazodin, 57
 Chlorobutanol-U S P (see N N R, 1950)
 Chloroguanide Hydrochloride, 197
 Chloromethapyriline Citrate, 9
 Chloromycetin, 142
 Chlorophenothane Ethyl Aminoben-
 zoate-Benzyl Benzoate, 87
 Chlorophyll Derivatives, Water-
 Soluble, 626
 Chloroprocaine Penicillin O, 175
 Chloroquine Phosphate, 198
 Chlorothen Citrate, 9
 Chlorotriarsene, 444
 Chlorpheniramine Maleate, 10
 Chlorophenpyridamine Maleate, 10
 Chlorotetracycline, 142
 Calcium, 143
 Hydrochloride, 144
 Chlor Trimeton Maleate, 10
 Cholera Vaccine-U S P (see N N R 1952)
 Choline Chloride, 528
 Derivatives, 233
 Dihydrogen Citrate, 529
 Gluconate, 530
 Cholinergic Blocking (Parasymp-
 atholytic) Agents, 262
 (Parasympathomimetic) Agents, 253
 Cholinesterase Inhibitors, 257
 Chondulendron Tomentosum Ex-
 tract, Purified, 562
 Chorionic Gonadotropin 474
 Choctyn Dihydrogen Citrate, 530
 Cinaphyl, 392
 Citrated Normal Human Plasma, 280
 Chitin Maleate, 9
 Clopane Hydrochloride, 223

- Cocculin, 347
 Coco Quinine (see N. N. R. 1949)
 Coal Liver Oil Concentrate (see N. N. R. 1952)
 with Vioosterol (see N. N. R. 1952)
 Codeine, 29
 Colloidal Silver Chloride N.F. (see N. N. R. 1950)
 Iodide-N.F. (see N. N. R. 1950)
 Combistrep, 196
 Compoicillin, 168
 Conestron, 443
 Conjugated Estrogens, 443
 Contra Creme, 351
 Contraceptive agents, evaluation of, xxxiv
 Capsules and Suppositories, 355
 Jellies and Creams, 350
 Contraceptives, 349
 Apparatus for Use With, 350
 Cooper Creme, 355
 Coparaffinate, 81
 Corlutone, 455
 Cortef, 427
 Acetate, 429
 Corticotropin, 469
 Purified, 471
 Cortisone Acetate, 423
 Cortogen Acetate, 424
 Cortone Acetate, 424
 Cortril, 427
 Acetate, 429
 Cotinazin, 101
 Creamalin, 402
 Crema-Bismuth (see N. N. R. 1949)
 Cresatin-Sulzberger (see N. N. R. 1951)
 m-Cresylacetate (see N. N. R. 1951)
 Crystalline Penicillin G Sodium, 174
 Crystodigin (see N. N. R. 1950)
 Cumerilin, 382
 Sodium, 383
 Cumopyran, 289
 Curare, 559
 Curariform Drugs, Antagonists of, 567
 Cutaneous Immunity Tests, Agents for, 509
 Cyancobalamin, 577
 Cyclaine Hydrochloride, 48
 Cyclamate Calcium, 538
 Sodium, 539
 Cyclobarbitol-N.F. (see N. N. R. 1951)
 Cyclocumarol, 288
 Cyclogyl Hydrochloride, 264
 Cyclopentamine Hydrochloride, 222
 Cyclopentolate Hydrochloride, 262
 Cyclopropane, 35
 Cyerimine Hydrochloride, 264
 Decholin (see N. N. R. 1953)
 Sodium (see N. N. R. 1953)
 Dehydrocholate Sodium N.F. (see N. N. R. 1953)
 Dehydrocholic Acid U.S.P. (see N. N. R. 1953)
 Delvinal Sodium, 340
 Demerol Hydrochloride, 27
 Depressants and Stimulants, Central Nervous System, 323
 Heart Muscle, 306
 Dermal Drying Agents, 618
 Dermatologic preparations of antihistamine drugs, xxxix
 Desoxycorticosterone Acetate, 418
 Desoxycortone Acetate, 418
 Desoxyephedrine Hydrochloride, 250, 252
 Desoxyn Hydrochloride, 231
 Dexedrine Sulfate, 222
 Dexoval Hydrochloride, 232
 Dextran, 292
 Dextro Amphetamine Sulfate, 221
 Dextrose, 527
 Diacetyl Morphine, 29
 Diagnex, 361
 Diagnostic Aids, 357
 Dial (see N. N. R. 1951)
 Diallylbarbituric Acid N.F. (see N. N. R. 1951)
 Dia Mer-Sulfonamides (see Sulfadiazine and Sulfamerazine)
 Diamertine, 127
 Diaparene Chloride, 78
 Diasone Sodium, 132
 Diatrine Hydrochloride, 13
 Dibucaine Hydrochloride, 44
 Dicumarol, 287
 Dicurin Procaine, 386
 Dienestrol, 445
 Diethylstilbestrol, 446
 Dipropionate, 450
 Digalen (see N. N. R. 1952)
 Digifolin (see N. N. R. 1952)
 Digilanid, 303
 Digitaline Nativele (see N. N. R. 1950)
 Digitalis and Related Principles, 301
 Digitoxin U.S.P. (see N. N. R. 1950)
 Diglycoell Hydroiodide-Iodine, 59
 Digoxin, 304
 Dihydrocodeinone Bitartrate, 31
 Dihydromorphinone Hydrochloride U.S.P. (see N. N. R. 1954)
 Dihydrostreptomycin and Streptomycin, 180
 Sulfate, 182
 Dihydrotheelin, 433
 Dihydroxyaluminum Aminoacetate, 406
 Diiodohydroxyquin, 213
 Diiodohydroxyquinoline, 213
 Dilantin Sodium, 341

- Dilaudid Hydrochloride (see N N R. 1954)
 Dimenformon Benzoate, 439
 Dimenhydrinate, 624
 Dimercaprol, 613
 Dimethisoquin Hydrochloride, 46
 Dimethyl Tubocurarine Chloride, 563
 Iodide, 564
 Dimethylhexecol Dipropionate, 451
 Dimothyn, 407
 Diodoquin, 214
 Diodrast (see N N R 1954)
 Compound, 373
 Concentrated, 375
 Dioloxol, 556
 Diothane Hydrochloride (see N N R 1954)
 Di-Paralene Hydrochloride, 9
 Diperonon Hydrochloride (see N N R 1954)
 Diphenamyl Methylsulfate, 265
 Diphenhydramine Hydrochloride, 11
 Diphenylhydantoin Sodium, 340
 Diphtheria and Tetanus Toxoids, 493
 Alum Precipitated, 499
 Aluminum Hydroxide Adsorbed, 500
 with Pertussis Vaccine Combined, 506
 Alum Precipitated, 507
 Aluminum Hydroxide Adsorbed, 508
 Toxin, Diagnostic U S P (see N N R 1950)
 Toxoid U S P (see N N R 1950)
 Alum Precipitated U S P (see N N R 1954)
 Aluminum Hydroxide Adsorbed, 495
 Phosphate Adsorbed, 496
 and Pertussis Vaccine Combined, 504
 Alum Precipitated, 505
 Aluminum Hydroxide Adsorbed, 505
 Dip Pert Tet, 506
 Alhydrox, 509
 Dipsuasis, 505
 Alhydrox, 506
 Disodium Autothiomalate, 622
 Distreptocin, 193
 Disulfiram, 610
 Disulfyn, 127
 Diuretics, 377
 Divinyl Oxide, 38
 Doca Acetate, 419
 Doraxamin, 407
 Dorsacaine Hydrochloride, 43
 Dorsaphyllin, 393
 Dorsulfax, 125
 Doxyfed Hydrochloride, 232
 Doxylamine Succinate, 12
 Dramamine, 626
 Dressings, Burns, 617
 Dried Yeast-U S P. (see N N R. 1952)
 Drisdol, 601
 Duo-Sulfanyl, 126
 Duozine, 126
 Dusting Powder, Absorbable, 539
 Edrophonium Chloride, 567
 Efroxine Hydrochloride, 232
 Emollients, 409
 Emulsion Ointment Base, 543
 Enbin, 89
 Enteric-coated preparations, evaluation of, xxxv
 Enteromone, 475
 Enzodase, 393
 Enzymes, 394
 Ephedrine-U S P (see N N R. 1950)
 Hydrochloride-N F. (see N N R. 1950)
 Sulfate-U S P (see N N R 1950)
 Epinephrine-U S P (see N N R 1949)
 Ergometrine Maleate, 533
 Ergonovine Maleate, 535
 Ergot Preparations, 532
 Ergotamine Tartrate-U S P. (see N N R 1950)
 with Caffeine, 623
 Ergotrate Maleate, 536
 Erythrityl Tetranitrate N F. (see N N R 1950)
 Erythrocin Lactobionate, 150
 Stearate, 150
 Erythrol Tetranitrate (see N N R. 1950)
 Erythromycin, 146
 Ethyl Carbonate, 147
 Glucosheptonate, 148
 Lactobionate, 149
 Stearate, 150
 Esomid Chloride, 315
 Esterified Parent Estrogens, 433
 Stilbene Derivatives, 450
 Estinyl, 442
 Estradiol, 433
 Benzoate, 438
 Cyclopentylpropionate, 439
 Dipropionate, 440
 Fithinyl, 441
 Monobenzoate, 438
 Estrifol, 443
 Estriol, 434
 Estrogen, 430
 Estrogenic Substances, Conjugated, 443
 Estrogens, Conjugated, 443
 Derivatives of Parent, 441
 Esterified Parent, 438
 Nonsteroid, 444
 Unclassified Derivatives of, 452
 Parent, 433
 Steroid, 433
 Estrone, 435
 Sulfate, Piperazine, 443
 Estrugenone, 436

- Estrusol, 437
 Etamon Chloride, 273
 Ether, Vinyl, 38
 Ethinyl Estradiol, 441
 Ethyl Aminobenzoate-N.F. (see N.N.R. 1949)
 -Benzyl Benzoate-Chlorophenothane, 87
 Biscoumacetate, 289
 Chloride-U.S.P. (see N.N.R. 1949)
 Iodophenylundecylate Injection, 369
 -Morphine, 29
 Ethylene-U.S.P. (see N.N.R. 1950)
 Etycylol, 442
 Eucatropine Hydrochloride-U.S.P. (see N.N.R. 1950)
 Euphthalmine Hydrochloride (see N.N.R. 1950)
 Euquinine (see N.N.R. 1949)
 Euresol pro Capillis (see N.N.R. 1950)
 Evans Blue, 357
 Evipal Sodium, 330
 Evronal Sodium, 336
 Exorbin, 409
 Expandex, 283

 Flaxedil Triethiodide, 554
 Fluorescein Sodium-U.S.P. (see N.N.R. 1950)
 Folic Acid, 581
 Injection, 582
 Follutein, 475
 Forthane, 236
 Fructose, 526, 527
 Fuadin, 206
 Furacin, 67
 Furadantin, 105

 Gallamine Triethiodide, 553
 Gamma Benzene Hexachloride, 90
 Gamophen, 70
 Ganglionic Blocking Agents with both Parasympatholytic and Sympatholytic Actions, 272
 Gantrisin, 121
 Acetyl, 122
 Diethanolamine, 123
 Gas Gangrene Antitoxin, Bivalent-N.F. (see N.N.R. 1952)
 Pentavalent N.F. (see N.N.R. 1952)
 Trivalent-N.F. (see N.N.R. 1952)
 Gastric Acidity, Agents Used for Determination of, 359
 Mucin, 409
 Secretory Activity, Agents Used for Testing, 361
 Gastro-intestinal Agents, 400
 Gelatin Film, Absorbable, 540
 Sponge, Absorbable, 295
 Gelatine Solution, Special Intravenous, 284

 Gelfilm, 541
 Gelfoam, 296
 Gemomil, 333
 General Anesthetics, 35
 Gentran, 283
 Gexane, 91
 Gitaligin, 306
 Gitalin (Amorphous), 305
 Globin Insulin with Zinc, 461
 Zinc Insulin, 461
 Globulin, Immune Serum, 492
 Polio-myelitis Immune (Human), 494
 Gluco-corticoids, 419
 Glucophylline, 391
 Glycobiarsol, 207
 Glycotaurol (see N.N.R. 1949)
 Glynazan, 393
 Glytheonate, 393
 Gold Compounds, 619
 Sodium Thiomalate, 622
 Thiosulfate-N.F. (see N.N.R. 1951)
 Thioglucose, 621
 Gonadotropic Substances, 472
 Gonadotropin, Chorionic, 474
 Guanacol Hydrochloride, 198

 Halazone-N.F. (see N.N.R. 1952)
 Halibut Liver Oil with Viosterol (see N.N.R. 1953)
 Haliver Oil with Viosterol (see N.N.R. 1953)
 Halogen Compounds, 56
 Heart Muscle Depressants, 306
 Hedulin, 295
 Hemomin, 578
 Hemostatics, 295
 Heparin Sodium, 291
 Hexachlorocyclohexane, 90
 Hexachlorophene, 69
 Hexamethonium Bromide, 311
 Chloride, 313
 Hexameton Chloride, 314
 Hexamethylenamine Mandelate, 103
 Hexamethylenetetramine Mandelate, 103
 Hexavitamin, 609
 Hexestrol, 449
 Hexobarbital Sodium, 329
 Hex-O-San, 71
 Hexyleaine Hydrochloride, 47
 Hiohex Chloride, 315
 Hippuran (see N.N.R. 1954)
 Histamine Acid Phosphate, 361
 -Antagonizing Agents, 4
 Phosphate, 361
 Holocaine Hydrochloride (see N.N.R. 1950)
 Homatropine Hydrochloride (see N.N.R. 1950)
 Methylbromide, 267
 Hormones and Synthetic Substitutes, 415
 in allergy, 3
 Hyaluronidase, 394
 Hyazyme, 395
 Hyclorite (see N.N.R. 1950)

- Hycodan Bitartrate, 31
 Hydantoin Derivatives, 340
 Hydrabamine Penicillin G, 167
 Hydralazine Hydrochloride, 243
 Hydrocortisone, 425
 Acetate, 427
 Hydrocortisone, 427
 Acetate, 429
 Hydroxyamphetamine Hydro-
 bromide, 224
 Hyflavin, 589
 Hykinone, 605
 Hypertension, Agents Used in Dif-
 ferential Diagnosis of, 362
 Hyphylline, 389
 Hypotensive Agents, 308
 Hypotigen, 514
 Iletin (see N.N.R. 1950)
 Lente, 465
 NPH, 463
 Ilotycin, 147
 Ethyl Carbonate, 148
 Glucobionate, 149
 Immune Serum Globulin (Human),
 492
 Serums, 488
 Immunity Tests, Agents for Cu-
 taneous, 509
 Immunologic Agents, 487
 Incorporal, 124
 Infagen, 508
 Influenza Virus Vaccine, Poly-
 valent, 501
 Influenzae Type B Serum (Rab-
 bit), Anti-Hemophilus,
 489
 Insulin, 456
 Crystals, Zinc, 460
 Globin Zinc, 461
 Injection-U.S.P. (see N.N.R.
 1950)
 Isophane, 462
 Labeling Regulations, 459
 Lente, 463
 NPH, 462
 Preparations, Long-Acting, 461
 Protamine Zinc, 465
 Intocostrin, 363
 Invert Sugar, 527
 Iocamsen (see N.N.R. 1949)
 Iodakon (see N.N.R. 1950)
 Sodium (see N.N.R. 1950)
 Iodides, in allergy, 2
 Iodine and Derivatives, 58
 Compounds, 213
 for Roentgenography, Water
 Insoluble Organic, 367
 Water-Soluble Organic,
 371
 Iodized Oil U.S.P. (see N.N.R.
 1950)
 Poppy-Seed Oil 10% (see N.N.R.
 1950)
 Iodoalphonic Acid, 368
 Iodochlorhydroxyquin-U.S.P. (see
 N.N.R. 1952)
 Iodochlorhydroxyquinone (see
 N.N.R. 1952)
 Iodochlorol, 368
 Iodohippurate Sodium (see N.N.R.
 1954)
 Iodopanoic Acid, 369
 Iodophthalein Sodium U.S.P. (see
 N.N.R. 1950)
 Iodopyracet (see N.N.R. 1954)
 Compound, 372
 Concentrated, 373
 Iopanoic Acid, 369
 Iophendylate, 369
 Iothiouracil Sodium, 517
 Iprat Calcium (see N.N.R. 1951)
 Sodium, 333
 Isobornyl Thiocyanacetate-Techni-
 cal, 89
 Isoniazid, 99
 Isonicotinic Acid Derivatives, 99
 Isonorin Sulfate, 227
 Iso-Par, 82
 Isophane Insulin, 462
 Isophrin Hydrochloride (see N.N.R.
 1954)
 Isopropylarterenol Hydrochloride,
 225
 Sulfate, 227
 Isoproterenol Hydrochloride, 225
 Sulfate, 227
 Isotopes, Radioactive, 545
 Isuprel Hydrochloride, 226
 Itrium Sodium, 519
 Kelene (see N.N.R. 1949)
 Kidney Function Tests, Agents
 Used for, 364
 Kondremul (see N.N.R. 1949)
 Konogen, 443
 Konsyl, 413
 Koromex Cream and Jelly, 352,
 353
 Kwell, 91
 Label and labeling, definition of,
 xii
 Lac Bismo (see N.N.R. 1949)
 Lactate One-Sixth Molar (see
 N.N.R. 1949 under
 Sodium Lactate Injec-
 tion U.S.P.)
 Lactated Potassic Saline, 530
 Ringer's Solution U.S.P. (see
 N.N.R. 1947)
 Lactikol Creme and Jelly, 351
 Lactobavin, 589
 Lantene Jelly, 352
 Lauron, 622
 Laxatives and Cathartics, 409
 Lenigallol (see N.N.R. 1951)
 Lente Iletin, 465
 Insulin, 463
 Levarterenol Bitartrate, 228
 Levo-Dromoran Tartrate, 32
 Levophed Bitartrate, 210
 Levorphanol Tartrate, 11
 Levugen, 527
 Levulose, 526

- Lidocaine Hydrochloride, 49
 Lindane, 90
 Lipiodol Radiologique Ascendant
 (see N.N.R. 1950)
 Lipotropic Agents, 528
 Liqueamin Sodium, 293
 Liquid Petrolatum Emulsion-N.F.
 (see N.N.R. 1949)
 Liver Oil, Percomorph, 608
 Local Anesthetics, 39
 Anti-infectives, 54
 Lorophyn Jelly, 352
 Suppositories, 356
 Luminal (see N.N.R. 1949)
 Sodium (see N.N.R. 1952)
 Lunosol (see N.N.R. 1950)
 Lutrexin, 453
 Lututrin, 453
 Lygel Vaginal Jelly, 353
 Lygenes Vaginal Suppositories,
 356
 Lynoral, 442

 Magma Alzinol, 407
 Magnamycin, 140
 Magnesium Phosphate, Tribasic-
 N.F. (see N.N.R.
 1947)
 Trisilicate-U.S.P. (see N.N.R.
 1947)
 Mandelamine, 104
 Mandelic Acid, 102
 Derivatives, 102
 Manna Sugar, 364
 Mannite, 364
 Mannitol, 364
 Hexanitrate, 320
 Marvosan Creme, 355
 Measles Convalescent Serum, 490
 Immune Serum, Human, 490
 Prophylactic, 493
 Mebaral, 332
 Mecholy Bromide, 255
 Chloride, 257
 Mecostrin Chloride, 564
 Medinal (see N.N.R. 1949)
 Menadiol Sodium Diphosphate, 602
 Menadiolone, 603
 Sodium Bisulfite, 605
 Menaphthene, 603
 Menaphthone, 603
 Meonine, 517
 Mepacrine Hydrochloride, 199
 Meperidine Hydrochloride, 25
 Mepharsen, 211
 Mephensesin, 554
 Mepherol, 556
 Mephobarbital, 330
 Mephson, 557
 Mephyton, 607
 Meprane Dipropionate, 452
 Metalluride Sodium, 380
 Merbak, 62
 Merbromin-N.F. (see N.N.R. 1950)
 Mercaptomerin Sodium, Sterile, 380
 Mercocresols, 62
 Mercresin, 63
 Mercuhydrin Sodium, 380

 Mercumatilin, 382
 Sodium, 382
 Mercuric Iodide, Potassium-N.F.
 (see N.N.R. 1950)
 Mercurochrome (see N.N.R. 1950)
 Mercurophylline, 383
 Sodium, 383
 Mercury, 60
 Compounds, 378
 Mercuzanthin (Sodium), 384
 Mer-Diazine, 127
 Merdisul, 126
 Merethoxylline Procaine, 385
 Merphenyl Nitrate, 64
 Mersaly and Theophylline Injec-
 tion (and Tablets),
 386
 Sodium and Theophylline, 386
 Mersalyn, 387
 Merthiolate (see N.N.R. 1950)
 Mesopin, 268
 Metabolic Disorders, Agents Used
 in, 511
 Metal Compounds, 60
 Poisoning, Antidotes for Heavy,
 613
 Metamucil, 413
 Metaphen (see N.N.R. 1950)
 Methacholine Bromide, 255
 Chloride, 255
 Methadon, 27
 Methadone Hydrochloride, 27
 Metha-Merdisazine, 130
 Methamphetamine Hydrochloride,
 230
 Methantheline Bromide, 268
 Methaphenylene Hydrochloride, 12
 Methapyriline Hydrochloride, 13
 Metharbital, 332
 Meth-Dia-Mer-Sulfonamides (see
 Trisulfapyrimidines)
 Methenamine-U.S.P. (see N.N.R.
 1949)
 Compounds, 103
 Mandelate, 103
 Methergine Tartrate, 537
 Methiacil, 520
 Methimazole, 519
 Methiodal Sodium-U.S.P. (see
 N.N.R. 1952)
 Methionine, 516
 Methum Chloride, 313
 Methoxamine Hydrochloride, 232
 Methoxyphenamine Hydrochloride,
 234
 Methylbenzethonium Chloride, 77
 Methylcellulose, 411
 Methylene Resin Polyamine, 408
 Methylergonovine Tartrate, 536
 Methylglucamine-Theophylline, 390
 Methylhexaneamine, 235
 Methylol Riboflavin, 589
 Methyltestosterone, 477
 Methylthiouracil, 519
 Mettione, 517
 Metopon Hydrochloride, 32
 Metrazol (see N.N.R. 1950)
 Metric system, xlv1

- Metubine Iodide, 565
 Metycaine Hydrochloride (see N N R. 1954)
 Migraine, Agents for Relief of, 623
 Mild Silver Protein-N.F. (see N N R 1949)
 Milibis, 208
 Mineral waters, xxxix
 Mixed Vitamin B Components, 595
 Vitamins, 607, 609
 Mixtures, Antibiotic, 192
 evaluation of, xxxvi
 Sulfonamide, 123
dl Monobasic Amphetamine Phosphate, 217
 Monocaine Formate, 43
 Hydrochloride, 44
 Morphine, 29
 Motion Sickness Remedies, 624
 Muciloid with Dextrose, Psyllium Hydrophilic, 413
 Mucin, Gastric, 409
 Mucotin, 408
 Multazine, 129
 Multifuge Citrate, 94
 Muracil, 520
 Mycfradin Sulfate, 153
 Myochrysine, 623
 Myoxane, 555
 Naepaine Hydrochloride, 51
 Nalline Hydrochloride, 34
 Nalorphine Hydrochloride, 33
 Naphazoline Hydrochloride, 236
 Naprylate, 80
 Nasal inhalant preparations containing petrolatum, xxxix
 Natural Vitamin A in Oil, 573
 Nembutal, 333
 Calcium, 334
 Sodium (see N N R 1952)
 Neo-Antergan Maleate, 16
 Neoarsphenamine N.F. (see N N R 1949)
 Neocinchophen N.F. (see N N R 1947)
 Neodrol, 478
 Neohetramine Hydrochloride, 16
 Neohydrin, 379
 Neo-Iopax (see N N R 1954)
 Neomycin, 150
 -Bacitracin, 192
 Sulfate, 151
 Neon (see N N R 1951)
 Neosalvarsan (see N N R 1949)
 Neo-Silvol (see N N R 1950)
 Neostam Stilbamine Glucoside, 205
 Neostigmine Bromide, 259
 Methylsulfate, 260
 Neo-Synephrine Hydrochloride (see N N R 1934)
 Neothylline, 390
 Niacin, 584
 Nicotinamide, 583
 Niadrin, 101
 Nicotinamide, 583
 and Nicotinic Acid, 583
 Nicotinic Acid, 584
 Amide, 583
 and Nicotinamide, 583
 Nicotizide, 101
 Nikethamide, 345
 Nisentil Hydrochloride, 25
 Nisulfazole, 118
 Nitrates, Organic, 319
 Nitrofurans Derivatives, 65, 104
 Nitrofurazone, 65
 Nitromersol-N.F. (see N.N.R. 1950)
 Nitrosulfathiazole (see Paracetamol Nitrosulfathiazole)
 Nitrosulfathiazole, 24
 Nonopiate, Adding Analgesics, 24
 Nonsteroid Estrogens, 444
 Unclassified Derivatives of, 452
 Norepinephrine Bitartrate, 228
 Norisodrine Sulfate, 227
 Normal Human Plasma, 280
 Serum, 281
 Albumin, 278
 Serum Albumin (Human), 278
 Norodin Hydrochloride, 231
 Novatrin, 268
 Novocaine (see N N R. 1949)
 NP11 Hctin, 463
 Insulin, 462
 Nupercaine Hydrochloride, 45
 Nydrizid, 101
 Ointment Bases, 542
 Old Tuberculin-U.S.P. (see N N R. 1950)
 Oleaginous Ointment Base, 543
 Oleovitamin A, 573
 and D, Concentrated, 607
 D, Synthetic U.S.P. (see N N R 1952)
 Oleum Percomorphum, 608
 Ophthalmic use, solutions and suspensions for, xxxix
 Opium Principles and Derivatives, 29
 Oradiol, 442
 Oranixon, 556
 Orestalyn, 442
 Organic Iodine Compounds for Roentgenography, 367
 Water-Insoluble, 367
 Water-Soluble, 371
 Nitrates, 319
 Ortho-Creme Vaginal Cream, 353
 Ortho-Gynol Vaginal Jelly, 354
 Orthoxine Hydrochloride, 235
 Ouahain-U.S.P. (see N N R 1950)
 Ovaries, 429
 Ovocylin, 434
 Benzate, 439
 Dipropionate, 441
 Ox Bile Extract N.F. (see N N R 1949)
 Oxazolidine Derivatives, 342
 Oxidized Cellulose, 296
 Oxophenarsine Hydrochloride, 210
 Oxyel, 298

- Oxygen-Carbon Dioxide Mixtures (see N.N.R. 1947)
- Oxytetracycline, 153, 154
Hydrochloride, 154
-Polymyxin B, 193
- Oxytocics, 532
- Oxytocin-U.S.P. (see N.N.R. 1952)
- Pagitan Hydrochloride, 265
- Palatizine, 129
- Pancreas, 456
- Pantopique, 371
- Papaverine Hydrochloride-U.S.P. (see N.N.R. 1947)
- Para-Aminosalicylate Calcium, 97
Sodium, 97
- Para-Aminosalicylic Acid, 95
- Paradione, 342
- Paraffin, Pliable (see N.N.R. 1952)
- Paramethadione, 342
- Paraminyl Maleate, 15
- Para Nitrosulfathiazole, 117
- Para Pas, 96
Sodium, 98
- Parasal, 96
Sodium, 98
- Parasympatholytic and Sympatholytic Actions, Ganglionic Blocking Agents with both, 272
(Cholinergic Blocking) Agents, 262
- Parasympathomimetic (Cholinergic) Agents, 253
- Parathyroid Injection U.S.P. (see N.N.R. 1950)
- Paredrine Hydrobromide, 225
- Parentamine, 515
- Parent Estrogens, 433
Derivatives of, 441
Esterified, 438
- Parenteral Fluids, 530
use, therapeutic agents derived from animal sources for, xi
- Paroidin (see N.N.R. 1950)
- Parresine (see N.N.R. 1952)
- PAS, 95
- Pasara Sodium, 98
- Pasem Sodium, 98
- Pasmed Sodium, 98
- Penicillin, 158
and sulfonamide preparations for topical applications, xxxix
for Inhalation, 161
Injection for Prolonged Action, 164
for Prompt Action, 163
Oral or Sublingual Administration, 162
Aluminum, 164
G, Benzathine, 164
Hydrabamine, 167
Potassium, 168
Procaine, 172
Sodium, 174
- Penicillin—(Continued)
O, Chloroprocaine, 175
Potassium, 176
Potassium, Benzyl, 168
Sodium, Benzyl, 174
- Pentaerythritol Tetranitrate, 321
- Pentavalent Arsenic, Compounds Containing, 206
Gas Gangrene Antitoxin-N.F. (see N.N.R. 1952)
- Pentobarbital, 333
Calcium, 333
Sodium-U.S.P. (see N.N.R. 1952)
- Pentonal Sodium, 339
- Pentylene tetrazole-U.S.P. (see N.N.R. 1950)
- Percomorph Liver Oil, 608
- Peritrate Tetranitrate, 322
- Permapen, 166
- Peroxide, Zinc, Medicinal, 68
- Peroxides, 67
- Pertussis Immune Human Serum, 491
Serum (Human), 491
- Vaccine, 502
Alum Precipitated, 503
Aluminum Hydroxide Adsorbed, 504
and Diphtheria Toxoid Combined, 504
Alum Precipitated, 505
Aluminum Hydroxide Adsorbed, 505
Combined, Diphtheria and Tetanus Toxoids with, 506
Alum Precipitated, 507
Aluminum Hydroxide Adsorbed, 508
- Petrobran (see N.N.R. 1949)
- Petrogalar (see N.N.R. 1949)
- Petrolatum Emulsion, Liquid N.F. (see N.N.R. 1949)
- Phanoxorn (see N.N.R. 1951)
- Pharmaceutic and Therapeutic Aids, 538
- Phemerol Chloride, 76
- Phenacaine Hydrochloride-N.F. (see N.N.R. 1950)
- Phenacemide, 344
- Phenarsone Sulfoxylate, 208
- Phenindione, 294
- Pheniramine Maleate, 14
- Phenobarbital U.S.P. (see N.N.R. 1949)
Sodium-U.S.P. (see N.N.R. 1949)
- Phenol Derivatives, 69
- Phentolamine Hydrochloride, 246
Methanesulfonate, 248
- Phenurone, 345
- Phenylacetylurea, 344
- Phenylbutazone, 19
- Phenylephrine Hydrochloride-U.S.P. (see N.N.R. 1954)
- Phenylmercuric Nitrate, 63

- Phenylpropanolamine
 Hydrochloride, 237
 Phenylpropylmethylamine, 238
 Hydrochloride, 239
 Phenytoin Sodium, 340
 pifisoiler, 71
 Phosphaljel, 403
 Phthalylsulfathiazole, 118
 Pytonadione, 606
 Picragol, 65
 Picrotoxin, 347
 Piperat Tartrate, 94
 Piperazine Citrate, 93
 Estrone Sulfate, 443
 Tartrate, 94
 Piperocaine Hydrochloride U S P
 (see N N R 1954)
 Pipetoxan Hydrochloride, 363
 Pitocin (see N N R 1952)
 Pitressin (see N N R 1950)
 Tannate, 472
 Pituitary Gland, 467
 Posterior U S P (see N N R
 1949)
 Pituitrin (see N N R 1950)
 Placenta, 472
 Plague Vaccine N F (see N N R
 1950)
 Plantago Ovata Coating, 413
 Plasma, Antihemophilic, (Human),
 279
 Normal Human, 280
 Substitutes, 282
 and Blood Derivatives, 274
 Flavolex, 283
 Poisoning, Antidotes for Heavy
 Metal, 613
 Poliomyelitis Immune Globulin
 (Human), 494
 Polyamine Methylene Resin, 408
 Polyethylene Glycol, 300, 543
 400, 543
 1000, 543
 1500, 544
 1540, 544
 4000, 544
 Polymyxin, 177
 B Oxytetracycline, 193
 Sulfate, 378
 Polyvalent Influenza Virus Vaccine,
 501
 Pontocaine Hydrochloride, 53
 Poppy Seed Oil 10%, Isotized (see
 N N R 1952)
 Posterior Lobe, 468
 Pituitary U S P (see N N R
 1949)
 Extracts, 533
 Potassium Saline, Lactated 530
 Potassium Mercuric Iodide-N F
 (see N N R 1950)
 Penicillin G, 168
 O, 176
 Prantal Methylsulfate, 267
 Premarin, 443
 Primolan, 368
 Priscoline Hydrochloride, 252
 Prizine Hydrochloride, 237
 Probarbital Calcium (see N N R,
 195E)
 Sodium, 334
 Probenecid, 614
 Procainamide Hydrochloride, 306
 Procaine Amide Hydrochloride, 306
 Hydrochloride-U S P (see
 N N R 1949)
 Penicillin G, 172
 Progesterone, 432, 454
 Promethestrol Dipropionate, 451
 Pronestyl Hydrochloride, 308
 Propadrine Hydrochloride, 238
 Propata, 96
 Prophepyridamine Maleate, 14
 Propion Gel, 84
 Propionate-Caprylate Mixtures, 82
 Compound, 83
 Propionic Acid, 82
 Propylhexedrine, 240
 Propylthiouracil, 520
 Prostigmin Bromide, 260
 Methylsulfate, 261
 Protamine Zinc Insulin, 465
 Protargol (see N N R 1949)
 Protein Derivative of Tuberculin,
 Purified, 509
 Hydrolysates and Amino Acid
 Preparations, 511
 Intravenous, 512
 Oral, 515
 Protoveratrine A and B, 315
 Maleates, 318
 Provell Maleate, 319
 Psyllate Sodium, 549
 Psyllium Hydrophilic Mucloid with
 Dextrose, 413
 Pteroylglutamic Acid, 581
 Purified Corticotropin, 471
 Protein Derivative of Tuberculin,
 509
 Parodigm (see N N R 1950)
 Pyramal Maleate, 15
 Pyramidon (see N N R 1949)
 Pyrethrum, 92, 93
 Pyribenzamine Citrate, 17
 Hydrochloride, 18
 Pyridoxine, 586
 Hydrochloride, 587
 Pyrilamine Maleate, 14
 Pyrimidine Derivatives, 108
 Pyrazidin, 101
 Quehim Chloride, 559
 Quinacrine Hydrochloride, 199
 Quinine Carbaerylic Resin, 359
 Ethylcarbonate (see N N R
 1949)
 Sulfate U S P (see N N R
 1949)
 Quotane Hydrochloride, 47
 Rabies Vaccine-U S P (see N N R
 1950)
 Racemic Amphetamine Phosphate,
 217
 Sulfate, 218

- Tetracycline, 188
 Hydrochloride, 189
 Tetracyn, 188
 Hydrochloride, 190
 Tetraethylammonium Chloride, 272
 Tetraiodophenolphthalein Sodium
 (see N.N.R. 1950)
 Theelin, 435
 Theelol, 434
 Thelestrin, 436
 Thenylene Hydrochloride, 13
 Theobromine Calcium Salicylate-
 N.F. (see N.N.R. 1948)
 Sodium Acetate-U.S.P. (see
 N.N.R. 1948)
 Theocalcin (see N.N.R. 1948)
 Theocin (see N.N.R. 1949)
 Soluble (see N.N.R. 1950)
 Theoglycinate, 392
 Theophylline (see N.N.R. 1949)
 Anhydrous, 185
 and Mersalyl Sodium, 386
 Sodium Acetate-N.F. (see
 N.N.R. 1950)
 Compounds, 389
 -Methylglucamine, 390
 Sodium Glycinate, 391
 Therapeutic Agents, Miscellaneous,
 610
 and Pharmaceutical Aids, 538
 Thesodate (see N.N.R. 1948)
 Thiamine, 591
 Hydrochloride, 591
 Thiamylal Sodium, 336
 Thimecil, 520
 Thimerosal N.F. (see N.N.R. 1950)
 Thio-Bismol (see N.N.R. 1952)
 Thiomerin Sodium, 381
 Thiopental Sodium, 338
 Thiopentone Sodium, 338
 Thonzylamine Hydrochloride, 16
 Thrombin, 298
 Thylogen Maleate, 15
 Thylose Sodium, 414
 Thymol Iodide N.F. (see N.N.R.
 1949)
 Thyroid, 484
 Titalac, 404
 Tolansin, 556
 Tolazoline Hydrochloride, 250
 Tolonium Chloride, 298
 Tolserol, 557
 Tolulox, 556
 Topical applications, penicillin and
 sulfonamide prepara-
 tions for, xxxix
 Toxoids, 495
 and Vaccines, Combinations of,
 504
 Combinations of, 498
 Travamin, 514
 Travert, 528
 Triasyn B, 595
 Tribasic Calcium Phosphate-N.F.
 (see N.N.R. 1947)
 Magnesium Phosphate-N.F. (see
 N.N.R. 1947)
 Tribromoethanol, 37
 Tribromoethyl Alcohol, 37
 Trichloroethylene, 22
 Tricombisul, 125
 Tridione, 343
 Tridipgen, 506
 Alum Precipitated, 507
 Trifonamide, 131
 Trihexyphenidyl Hydrochloride, 270
 Trilene, 24
 Trimethadione, 342
 Trimethylene, 35
 Trimeton Maleate, 14
 Trinavac, Alum Precipitated, 508
 Trionamide, 129
 Tripazine, 129
 Tripelennamine Citrate, 16
 Hydrochloride, 17
 Tri-Sulfameth, 129
 Trisulfapyrimidines, 127
 Trisulfazine, 129
 Trivalent Arsenic, Compounds Con-
 taining, 208
 Gas Gangrene Antitoxin N.F.
 (see N.N.R. 1952)
 Tromexan Ethyl Acetate, 291
 Truozine, 128
 Tuamine, 242
 Sulfate, 243
 Tuaminoheptane, 242
 Sulfate, 242
 Tuberculin, Old-U.S.P. (see N.N.R.
 1950)
 P.P.D., 509
 Purified Protein Derivative of,
 509
 Tubocurarine Chloride, 565
 Dimethyl, 563
 Iodide, Dimethyl, 564
 Typhoid Vaccine-U.S.P. (see
 N.N.R. 1950)
 Tyrothricin, 55
 Tyvid, 101

 Undecylenic Acid, 85, 86
 Undesol, 87
 Unidigin (see N.N.R. 1950)
 Urea-U.S.P. (see N.N.R. 1950)
 Urecholine Chloride, 255
 Urokon Sodium, 376
 Urotropin (see N.N.R. 1949)

 Vaccines, 500
 and Toxoids, Combinations of,
 504
 Vanzoate, 92
 Varidase, 399
 Vasoconstrictors, in allergy, 1
 Vasopressin Injection-U.S.P. (see
 N.N.R. 1950)
 Tannate, 472
 Vasoxy Hydrochloride, 234
 Ventriculin (see N.N.R. 1952)
 Veralba, 318
 Veriloid, 311
 Veritas Krems, 355
 Vermifugal Agents, 93
 Veronal (see N.N.R. 1949)

- Vibalt, 579
- Vibenate, 541
- Vinactane Sulfate, 392
- Vinbarbital Sodium, 339
- Vinethene, 39
- Vinyl Ether, 38
- Vioem Sulfate, 192
- Vioform (see N N R 1952)
- Viomycin, 190
- Sulfate, 190
- Viosterol, Halibut Liver Oil with
(see N N R 1953)
- in Oil (see N N R 1952)
- Vitamin A, 572
 - in Oil, Natural, 573
 - Water-Miscible, 574
- B Complex, 575, 576
 - Components, Mixed, 595
- B₁, 591
- B₂, 588, 589
- B₆, 586
- B₁₂, 577
 - with Intrinsic Factor Concentrate, 579
- C, 595
- D, 598
- D₂, 599
- E, 601
- G, 589
- K, 601
- K₁, 606
- Vitamins, 570
 - A and D, Preparations of, 607
 - Mixed, 607, 609
- Vonedrine, 239
 - Hydrochloride, 239
- Water-Insoluble Organic Iodine Compounds for Roentgenography, 367
- Water-Miscible Vitamin A, 574
- Water-Soluble Chlorophyll Derivatives, 626
 - Ointment Base, 545
- Organic Iodine Compounds for Roentgenography, 371
- Vitamin A (see Water-Miscible Vitamin A)
- Whooping Cough Vaccine, 502
- Wound Protectives, 626
- Wydase, 396
- Xanthine Derivatives, 387
- Xylacaine Hydrochloride, 50
- Yeast, Dried U.S.P. (see N N R 1952)
- Yodoxin, 214
- Zephiran Chloride, 75
- Zinadon, 101
- Zinax Burn Dressing, 618
- Zincate Burn Dressing, 617
- Zinc Caprylate, 80, 82
 - Insulin Crystals, 460
 - Globin, 461
 - Protamine, 465
- Peroxide, Medacmal, 68
- Propionate, 82
- Undecylenate, 86
- Zinchlorundesal, 85
- Zincundecate, 86

for signs of argyria, and the urine for albumin and casts. In all vaginal insufflation in the pregnant female, the physician should exercise every precaution to prevent positive pressure in the vagina because of danger of breaking the enlarged veins and introducing air into the venous circulation.

Dosage.—Concentrations of 1 to 2 per cent are used in the form of compound powder and vaginal suppositories.

The compound powder is administered by means of an insufflator or other surgical "powder blower." The vaginal suppository containing 0.13 Gm. in a boroglyceride gelatin base is intended primarily to be used as an adjunct in the treatment of this condition.

WYETH LABORATORIES, INC.

Powder Picragol Compound 1%: 5 Gm. bottles. 1 per cent silver picrate in purified kaolin.

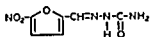
Vaginal Suppositories Picragol: 0.13 Gm. silver picrate in a boroglyceride gelatin base.

U. S. trademark 421,338

Nitrofuran Derivatives

The nitrofurans are substitution products of furan in which the 5-nitro group is essential for their antimicrobial activity. Depending largely on their concentration, they are bacteriostatic or bactericidal, probably through inhibition of enzymatic oxidative processes. Their bacteriostatic activity apparently results from a reversible inhibition of enzymes concerned with the dissimilation of pyruvate. The mechanism of the bactericidal action is unknown. In vitro, it is fairly difficult to develop bacterial strains that are resistant to nitrofurans. When such resistance occurs, it is of a relatively low degree. Cross resistance has been observed to some other 5-nitro-2-furaldehyde derivatives but not to chloramphenicol. Induced bacterial resistance to sulfathiazole, penicillin, chlortetracycline or streptomycin does not appear to entail resistance to the nitrofurans. Prolonged exposure to these compounds may produce sensitization in some patients.

The structural formula of nitrofurazone may be represented as follows.



Physical Properties.—Nitrofurazone is an odorless, lemon-yellow, crystalline powder, which turns brownish black on heating and decomposes between 236 and 240°. It is nearly tasteless but de-